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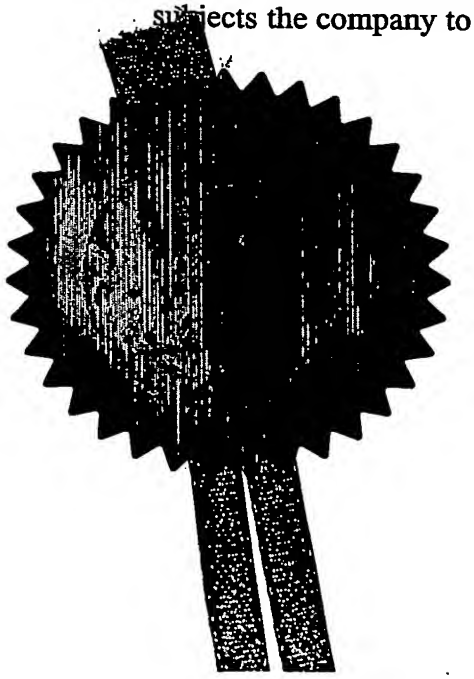
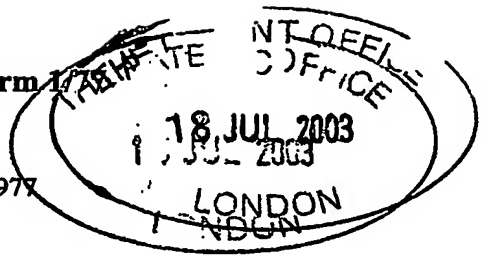


Signed P. Mahoney

Dated 24 June 2004

Patents Form 1/77



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1/77

Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

The Patent Office

Cardiff Road
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1.	Your Reference	RK/PB60403P
2.	Patent application number *(The Patent office will fill in this part)*	0316915.8
		21JUL03 E823808-1 D02029 P01/7700 0.00-0316915.8
3.	Full name, address and postcode of the or of each applicant *(underline all surnames)*	GLAXO GROUP LIMITED GLAXO WELLCOME HOUSE BERKELEY AVENUE GREENFORD MIDDLESEX UB6 ONN GB
	Patents ADP number *(if you know it)*	07358700 3
	If the applicant is a corporate body, give the country/state of its corporation	GB
4	Title of the invention	COMPOUNDS
5	Name of your agent *(if you know one)*	RIE KONDO
	"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*	GLAXOSMITHKLINE CORPORATE INTELLECTUAL PROPERTY CN925.1 980 GREAT WEST ROAD BRENTFORD MIDDLESEX TW8 9GS, GB
	Patents ADP number *(if you know it)*	8072555006

6. If you are declaring priority from one or more earlier patent applications, give the country and date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number	Country	Priority application number *(if you know it)*	Date of Filing (day / month / year)

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application	Number of earlier application	Date of filing (day / month / year)

8.	Is a statement of inventorship and of right to grant a patent required in support of this request? *(Answer yes if:* *a) any applicant named in part 3 is not an inventor, or* *b) there is an inventor who is not named as an applicant, or* *c) any named applicant is a corporate body.* *See note (d))*	YES

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	-
Description	51
Claim(s)	5
Abstract	-
Drawing(s)	-

10. If you are also filing any of the following, state how many against each item

Priority Documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patent Form 9/77)*	
Request for substantive examination *(Patent Form 10/77)*	
Any other documents *(please specify)*	

11. **I/We request the grant of a patent on the basis of this application**

Signature **RIE KONDO 18 July 2003**
AGENT FOR THE APPLICANTS

12. Name and daytime telephone number of person to contact in the United Kingdom

JEAN HARNEY

020 8047 4420

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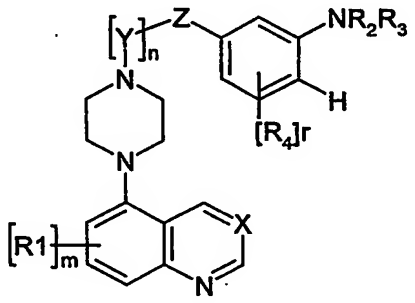
PB60403P

Compounds

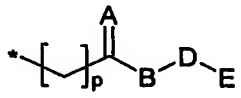
The present invention relates to novel compounds, processes for their preparation, pharmaceutical compositions containing the same and their use as medicaments in the treatment of CNS and other disorders.

A novel series of compounds has now been found that possess high affinity for 5-HT_1 type receptors and/or are 5-HT reuptake inhibitors. The present invention therefore provides, in a first aspect, a compound of formula (I) or a pharmaceutically acceptable salt thereof:



(I)

wherein:
R1 is halogen, cyano, C_{1-6}alkyl, C_{1-6}alkoxy, haloC1-6alkoxy or haloC_{1-6}alkyl;
m is 0, 1, 2, 3 or 4;
r is 0, 1, 2, 3 or 4;
X is N or CH;
n is 1, 2, 3 or 4;
Y is $-CH_2-$, -CH(C_{1-6}alkyl)- or -C(C_{1-6}alkyl)(C_{1-6}alkyl);
Z is $-CH_2-$, -CHOH-, -CHR5- or -CR5R6-;
R2 and R3 are independently hydrogen, C_{1-6}alkyl, C_{1-6}alkylsulfonyl or a group having the formula (II):



(II)

wherein p is 0, 1, 2, 3 or 4;
A is oxygen or sulfur;
B is a single bond or -NR7- wherein R7 is hydrogen, C_{1-6}alkyl or an optionally substituted aryl;
D is $-(CH_2)_q-$, $-(CH_2)_qO-$ or $-O(CH_2)_q-$, wherein q is 0, 1, 2, 3 or 4; and

E is C_{1-6}alkyl, haloC_{1-6}alkyl, an optionally substituted C_{3-7}cycloalkyl, an optionally substituted aryl, or E is -NR8R9 (wherein R8 and R9 are independently selected from hydrogen, C_{1-6}alkyl and optionally substituted aryl)

or R2 and R3, together with the nitrogen atom to which R2 and R3 are attached, combine to form an optionally substituted 3-7 membered monocyclic hetercyclic group;
and R4, R5 and R6 are independently halogen, cyano, C_{1-6}alkyl or C_{1-6}alkoxy.

The term "halogen" and its abbreviation "halo" refer to fluorine, chlorine, bromine or iodine.

The term "C_{1-6}alkyl" refers to an alkyl group having from one to four carbon atoms, in any isomeric form, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl and tert-butyl, pentyl, neopentyl, sec-pentyl, n-pentyl, isopentyl, tert-pentyl and hexyl.

The terms "haloC_{1-6}alkoxy" or "haloC_{1-6}alkyl" are used to describe a C_{1-6}alkoxy or a C_{1-6}alkyl group, respectively, substituted with one or more halogens. Examples include -$CHCl_2$, -CF_3, -OCF_3, etc.

The term "C_{1-6}alkylsulfonyl" refers to a group (C_{1-6}alkyl)-SO_2-. Examples include methylsulfonyl, ethylsulfonyl and propylsulphonyl.

The term "C_{3-7}cycloalkyl" refers to a cycloalkyl group consisting of from 3 to 7 carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. Optional substituents for C_{3-7}cycloalkyl includes one or more halogen, hydroxy, oxo, C_{1-6}alkyl, cyano, CF_3, OCF_3, C_{1-6}alkoxy and C_{1-6}alkanoyl.

The term "C_{1-6}alkoxy" refers to a straight chain or branched chain alkoxy (or "alkyloxy") group having from one to six carbon atoms, such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, tert-butoxy, pentoxy, neopentoxy, sec-pentoxy, n-pentoxy, isopentoxy, tert-pentoxy and hexoxy.

The term "C_{1-6}alkanoyl" refers to an alkanoyl group having from 1 to 6 carbon atoms, such as methanoyl (or "formyl"), ethanoyl (or "acetyl"), propanoyl, isopropanoyl, butanoyl, isobutanoyl, sec-butanoyl, pentanoyl, neopentanoyl, sec-pentanoyl, isopentanoyl, tertpentanoyl and hexanoyl.

The term "aryl", whether alone or as part of another group, is intended, unless otherwise stated, to denote , a 3- to 7- membered monocyclic aromatic ring or a 6- to 10- membered bicyclic aromatic ring, wherein one or more of the carbon atoms in the ring(s) is optionally replaced by a heteroatom independently selected from nitrogen, oxygen and sulfur. The 3- to 7- membered monocyclic aromatic ring or a 6- to 10- membered bicyclic aromatic ring may be optionally substituted by one or more substituents independently selected from halogen,

oxo, C_{1-6}alkyl, CF_3, cyano, hydroxy, C_{1-6}alkanoyl, and C_{1-6}alkoxy. Examples of monocyclic aryl groups include: phenyl, pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyrazolinyl, isothiazolyl, thiazolyl, isoxazolyl, furazanyl, furyl, thienyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, azepinyl and pyranyl. As used herein, the term "bicyclic aromatic ring" includes bicyclic ring systems in which both rings are aromatic, as well as bicyclic ring systems in which one of the rings is partially or fully saturated. Examples of bicyclic aryl groups include: naphthyl, indenyl, indolyl, isoindolyl, indazolyl, benzimidazolyl, benzoxazolyl, benzothienyl, benzuforanyl, dihydrobenzofuranyl, tetrahydrobenzofuranyl, quinolyl, quinoxalinyl, quinazolinyl, isoquinolyl, indazylyl, indanyl, tetrahydronaphthyl, indolinyl, isoindolinyl, tetrahydroisoquinolinyl, tetrahydroquinolyl, benzosazinyl, benzoxazinyl and benzoazepinyl. The term "aryl" as used herein covers all these groups. These groups may be attached to the rest of the molecule at any suitable position.

Where used herein the term naphthyl, whether alone or as part of another group, is intended, unless otherwise stated, to denote both 1-naphthyl and 2-naphthyl groups.

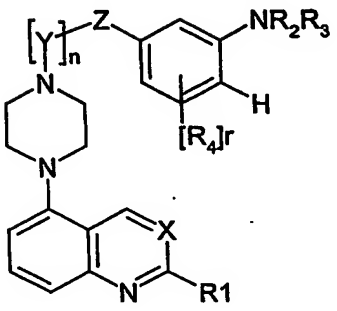
The term "oxo" refers to the group "=O".

The term "optionally substituted 3-7 membered monocyclic heterocyclic group" refers to a 3-7 membered, saturated, partially saturated or non-saturated ring containing 1, 2 or 3 heteroatoms selected from nitrogen, sulfur and oxygen. Examples of 5-7 membered monocyclic heterocyclic groups include pyrrolidinyl, imidazolidinyl, pyrazolidinyl, oxazolidinyl, isothiazolidinyl, thiazolidinyl, tetrahydrofuranyl, dioxolanyl, pyrrolyl, pyrrolinyl, pyrazolinyl, imidazolyl, pyrazolyl, isothiazolyl, thiazolyl, furyl, thienyl, piperidyl, piperazinyl, morpholinyl, tetrahydrothienyl, dioxanyl, thiomorpholinyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, azepinyl and azepanyl. 3-7 membered heterocyclic groups include, in addition to the above, aziridinyl, oxiranyl and azetidinyl. These groups may be attached to the rest of the molecule at any suitable position.

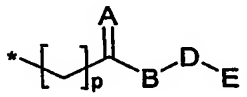
It is understood that, when R2 and R3 form an optionally substituted 3-7 membered monocyclic heterocyclic group together with the nitrogen atom to which R2 and R3 are attached, the 3-7 membered heterocyclic group is an N-linked 3-7 membered heterocyclic group. Examples of N-linked 3-7 membered heterocyclic group include aziridinyl, azetidinyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, isothiazolidinyl, thiazolidinyl, pyrrolyl, pyrrolinyl, pyrazolinyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, piperidyl, piperazinyl, morpholinyl, thiazinanyl, azepinyl and azepanyl.

All of these heterocyclic groups may be substituted by 1 to 4 substituents, which may be the same or different, and which is selected from halogen, oxo, C_{1-6}alkyl, cyano, CF_3, C_{1-6}alkoxy and C_{1-6}alkanoyl. The optional substituent(s) may be attached at any suitable position, including, where available, nitrogen atom(s).

In one embodiment, m is 1 and R1 is attached at the following position:



Each of R2 and R3 may independently be a group having the formula (II):



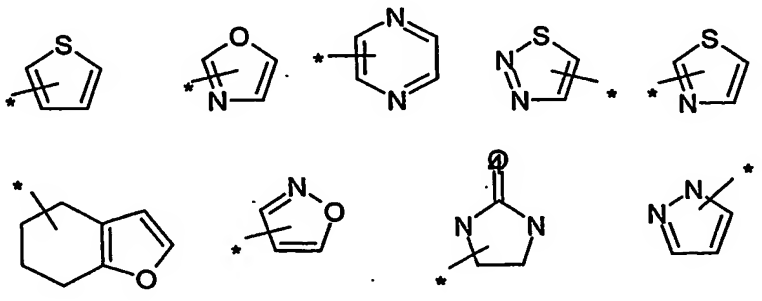
(II)

as defined above.

When E is -NR8R9 (wherein R8 and R9 are independently selected from hydrogen, C_{1-6}alkyl and aryl), examples of E include methylamine, ethylamine, propylamine, isopropylamine, butylamine, isobutylamine, sec-butylamine, tert-butylamine, pentylamine, neopentylamine, sec-pentylamine, n-pentylamine, isopentylamine, tert-pentylamine, hexylamine; dimethylamine, diethylamine, dipropylamine, diisopropylamine, dibutylamine, diisobutylamine, disec-butylamine, ditert-butylamine, dipentylamine, dineopentylamine, dihexylamine, butylmethylamino, isopropylmethylamino, ethylisopropylamino, ethylmethylamino; a monoarylamino such as anilino; and a monoC_{1-6}alkyl-monoarylamino such as -N(CH_3)phenyl.

When E is an optionally substituted aryl, it may be a 5- to 7- membered monocyclic aromatic ring, or a 9- to 10- membered bicyclic aromatic ring, wherein one or more of the carbon atoms in the ring(s) is optionally replaced by a heteroatom independently selected from nitrogen, oxygen and sulfur, wherein the ring is optionally substituted by one or more substituents independently selected from oxo, halogen, C_{1-6}alkyl, CF_3, cyano, hydroxy, C_{1-6}alkanoyl, and C_{1-6}alkoxy.

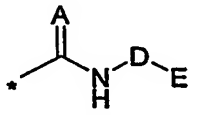
Suitable groups for E include optionally substituted 3-7 membered monocyclic heterocyclic groups such as :



These groups may be substituted, suitably by 1, 2 or 3 substituents selected from CF_3, C_{1-6}alkoxy, C_{1-6}alkyl, oxo and halogen.

In one embodiment, E is phenyl, optionally substituted by 1, 2 or 3 substituents selected from CF_3, C_{1-6}alkoxy, C_{1-6}alkyl and halogen.

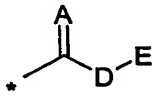
In one embodiment, formula (II) may be:



(IIa)

wherein A is oxygen or sulfur, D is $-(CH_2)_r-$, $-(CH_2)_rO-$ or $-O(CH_2)_r-$ wherein r is 0, 1, 2, 3, or 4, and E is C_{1-6}alkyl, an optionally substituted C_{3-7}cycloalkyl or an optionally substituted aryl ;

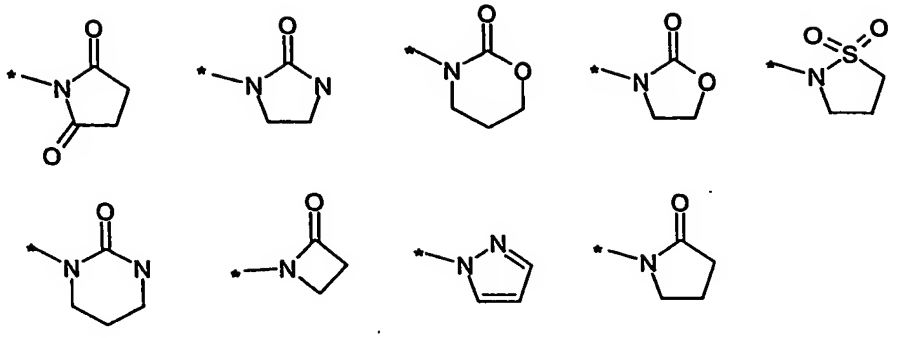
or



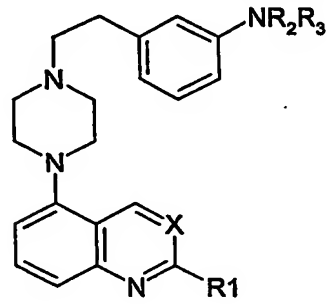
(IIb)

wherein A is oxygen or sulfur, D is $-(CH_2)_r-$, $-(CH_2)_rO-$ or $-O(CH_2)_r-$ wherein r is 0, 1, 2, 3, or 4, and E is C_{1-6}alkyl, an optionally substituted C_{3-7}cycloalkyl or an optionally substituted aryl group.

When R2 and R3, together with the nitrogen atom to which R2 and R3 are attached, combine to form an optionally substituted 3-7 membered monocyclic hetercyclic group, preferably it is a 4-6 membered monocyclic hetercyclic group, optionally substituted by one or more oxo. Suitable groups include:



In one embodiment, compounds of the present invention may have a general formula (Ia) :



(Ia)

wherein X, R1, R2 and R3 are as defined above.

Exemplary compounds of this invention include:

- 3-(3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}phenyl)-1,3-oxazolidin-2-one;
- *N*-(3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}phenyl)-*N'*-phenylurea;
- *N*-[2-(methyloxy)phenyl]-*N'*-(3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}phenyl)urea;
- 1-(3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}phenyl)-2-imidazolidinone;
- 2,4-dimethyl-*N*-(3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}phenyl)-1,3-thiazole-5-carboxamide;
- *N*-(3-{1-hydroxy-2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}phenyl)-2,4-dimethyl-1,3-thiazole-5-carboxamide;
- 2-fluoro-*N*-(3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}phenyl)benzamide

and pharmaceutically acceptable salts thereof.

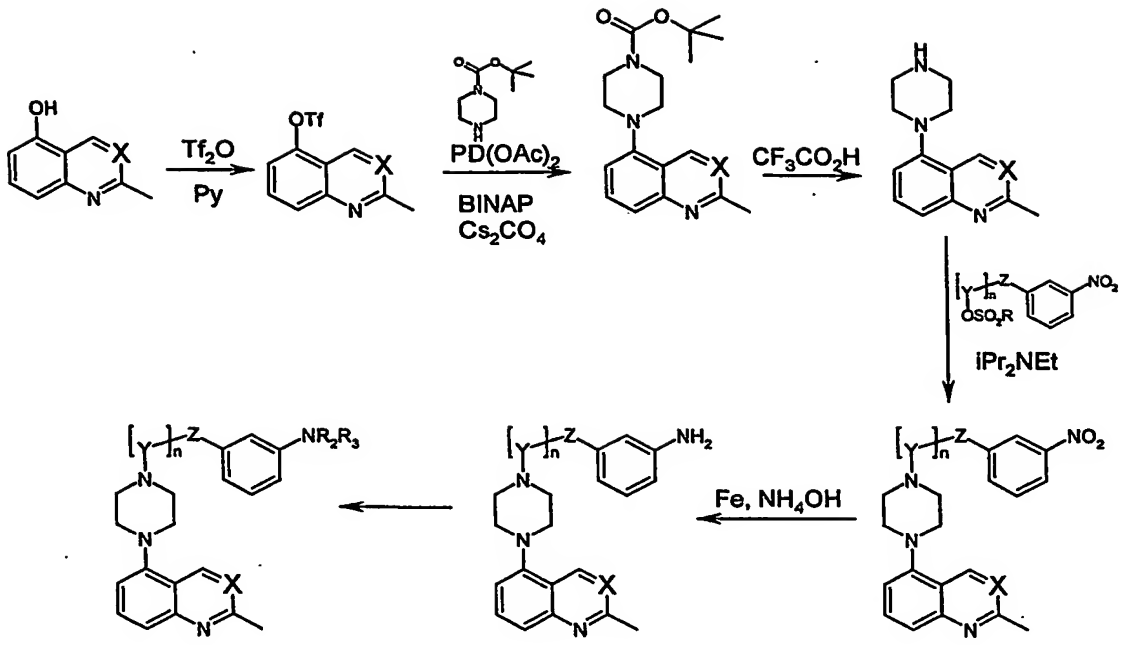
The compounds of formula (I) can form acid addition salts thereof. It will be appreciated that for use in medicine the salts of the compounds of formula (I) should be pharmaceutically acceptable. Suitable pharmaceutically acceptable salts will be apparent to those skilled in the art and include those described in J. Pharm. Sci., 1977, 66, 1-19, such as acid addition salts formed with inorganic acids e.g. hydrochloric, hydrobromic, sulfuric, nitric or phosphoric

acid; and organic acids e.g. succinic, maleic, acetic, fumaric, citric, tartaric, benzoic, p-toluenesulfonic, methanesulfonic or naphthalenesulfonic acid. Certain of the compounds of formula (I) may form acid addition salts with one or more equivalents of the acid. The present invention includes within its scope all possible stoichiometric and non-stoichiometric forms.

The compounds of formula (I) may be prepared in crystalline or non-crystalline form, and, if crystalline, may optionally be hydrated or solvated. This invention includes within its scope stoichiometric hydrates or solvates as well as compounds containing variable amounts of water and/or solvent.

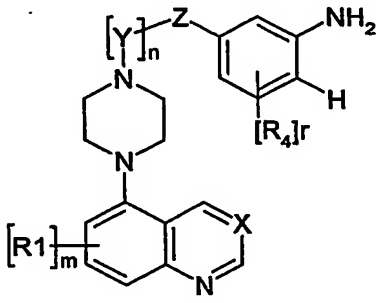
Certain compounds of formula (I) are capable of existing in stereoisomeric forms (e.g. geometric (or "*cis-trans*") isomers, diastereomers and enantiomers) and the invention extends to each of these stereoisomeric forms and to mixtures thereof including racemates. The different stereoisomeric forms may be separated one from the other by the usual methods, or any given isomer may be obtained by stereospecific or asymmetric synthesis. The invention also extends to any tautomeric forms and mixtures thereof. The present invention includes within its scope all such isomers, including mixtures.

Compounds of formula (I) may be prepared according to procedures described herein, or by analogous procedures thereto. A typical reaction route for a compound of formula (I) wherein m is 1 and R1 is methyl, and r is 0, is as follows:



The above reaction scheme may be adapted to prepare compounds of formula (I) wherein R1 is other than methyl, and in a position other than as illustrated above.

Thus, in a further aspect, this invention provides a process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt thereof, which process comprises reacting a compound of formula (III):



(III)

wherein R1, m, X, Y, n, Z, R4 and r are as defined for formula (I), with compound(s) containing appropriate functional group(s) which is/are capable of reacting with a compound of formula (III) to form a compound of formula (I);
and thereafter optionally:

- removing any protecting groups and/or
- converting a compound of formula (I) into another compound of formula (I) and/or
- forming a pharmaceutically acceptable salt.

Compounds of formula (I) can be converted into further compounds of formula (I) using standard techniques. For example, and by way of illustration rather than limitation, possible conversion reactions include acylation with an appropriate acylating agent such as acetyl chloride, alkylation using an appropriate alkylating reagent such as methyl iodide, and sulfonylation using a sulfonylating agent such as methanesulfonic anhydride.

Compounds of formula (III) may be prepared according to procedures described herein, by known literature methods, or by analogous procedures thereto.

It will be appreciated by those skilled in the art that it may be necessary to protect certain reactive substituents during some of the above procedures. Standard protection and deprotection techniques, such as those described in Greene T.W. *Protective groups in organic synthesis*, New York, Wiley (1981), can be used. For example, primary amines can be protected as phthalimide, benzyl, t-butyloxycarbonyl, benzyloxycarbonyl or trityl derivatives. Carboxylic acid groups can be protected as esters. Aldehyde or ketone groups can be protected as acetals, ketals, thioacetals or thioketals. Deprotection of such groups is achieved using conventional procedures well known in the art. For example, protecting groups such as t-butyloxycarbonyl may be removed using an acid such as hydrochloric or trifluroroacetic acid in a suitable solvent such as dichloromethane, diethylether, isopropanol or mixtures thereof.

Pharmaceutically acceptable salts may be prepared conventionally by reaction with the appropriate acid or acid derivative.

The affinities of the compounds of this invention for 5-HT_{1A}, 5-HT_{1B} and 5-HT_{1D} receptors can be determined by the following assay. CHO cells expressing 5-HT_{1A} receptors (4×10^7 cells/ml) are homogenised in Tris buffer and stored in 1ml aliquots. CHO cells expressing 5-HT_{1B} receptors (4×10^7 cells/ml) are homogenised in Tris buffer and stored in 1.5 ml aliquots. CHO cells expressing 5-HT_{1D} receptors (1×10^8/ml) are homogenised in Tris buffer and stored in 1 ml aliquots. 0.4 ml of a cell suspension is incubated with [^{3}H]-5-HT (4nM) for 5-$HT_{1B/1D}$ receptors and [^{3}H]WAY100635 (1nM) for 5-HT_{1A} receptors in Tris Mg HCl buffer (pH 7.7) and test drug, at 37°C for 45 minutes. Each test drug is tested at 10 concentrations (0.01 mM to 0.3 nM final concentration), with non-specific binding defined using 0.01 mM 5-HT. The total assay volume is 0.5 ml. Incubation is stopped by rapid filtration using a Packard Filtermate and radioactivity measured by Topcount scintillation counting. pKi values are calculated from the IC_{50} generated by an iterative least squares curve fitting programme.

All the Example compounds shown below were tested according to the radioligand binding assay described above and were found to have pKi values > 6.0 at 5-HT_{1A} receptors, with many showing a considerably higher affinity (having pKi values in the range 8.0 – 10.0)

Certain compounds of this invention also demonstrate comparable affinity for 5-HT_{1B} and 5-HT_{1D} receptors.

The intrinsic activity of the compounds of this invention can be determined according to the following assay. HEK293 cell membranes stably expressing human 5-HT_{1A} receptors and CHO cell membranes stably expressing human 5-HT_{1B} receptors are homogenised in HEPES/EDTA buffer and stored in 1ml aliquots, and [^{35}S]GTPγS binding studies are carried out essentially as described by Lazareno *et al.*, (Life Sci., 1993, **52,** 449) with some minor modifications. Membranes from 10^6 cells are pre-incubated at 30°C for 30 minutes in 20 mM HEPES buffer (pH 7.4) in the presence of $MgCl_2$ (3 mM), NaCl (100 mM), GDP (10μM) and ascorbate (0.2 mM), with or without test compounds. The reaction is started by the addition of 50 μl of [^{35}S]GTPγS (100 pM, assay concentration) followed by a further 30 minutes incubation at 30°C. Non-specific binding is determined using nonradiolabelled GTPγS (20 μM) added prior to the membranes. The reaction is terminated by rapid filtration through Whatman GF/B grade filters followed by 5 x 1 ml washes with ice cold HEPES (20 mM) /$MgCl_2$ (3 mM) buffer. Radioactivity is measured using liquid scintillation spectrometry. This procedure is hereafter referred to as the [^{35}S]GTPγS functional assay.

It has been found, using the [^{35}S]GTPγS functional assay, that certain compounds of formula (I) appear to be antagonists at 5-HT_1 type receptors whilst others appear to be inverse agonists, agonists or partial agonists.

The efficacy of the compounds of this invention to inhibit the re-uptake of serotonin can be measured in a 5-HT uptake assay by measurement of uptake of [^{3}H]-5-HT into LLCPK cells expressing human or rat serotonin transporters. In brief, cells are harvested and plated onto 96-well plates (10,000 cells per well). 24hr later cells are washed 2x with HBSSH (Hanks'balanced salt solution + 20mM HEPES). 50ul of test compound or vehicle is added to each well and incubated for 10min. Subsequently, [^{3}H]5-HT (final concentration 25nM) is added and the test mixture is incubated for a further 7min. The reaction is terminated by aspiration of test mixture and the cells are washed 6x with HBSSH. 50ul of scintillation cocktail (Microscint-20, Packard) is added onto the cells and the top and bottom of the plate is sealed. Plates are read, 30min later, in a Packard TopCount.

Some of the Example compounds tested according to this uptake assay were found to have potency at the uptake site of pIC_{50} of > 6.0.

Compounds of formula (I) and their pharmaceutically acceptable salts are of use in the treatment of certain CNS disorders such as depression (which term includes bipolar depression, unipolar depression, single or recurrent major depressive episodes with or without psychotic features, catatonic features, melancholic features, atypical features or postpartum onset, seasonal affective disorder and dysthymia, depressive disorders resulting from a general medical condition including, but not limited to, myocardial infarction, diabetes,

miscarriage or abortion), anxiety disorders (which includes generalised anxiety and social anxiety disorder), schizophrenia, panic disorder, agoraphobia, social phobia, obsessive compulsive disorder, post-traumatic stress disorder, pain (particularly neuropathic pain), memory disorders (including dementia, amnesic disorders and age-associated memory impairment), disorders of eating behaviours (including anorexia nervosa and bulimia nervosa), sexual dysfunction, sleep disorders (including disturbances of circadian rhythm, dyssomnia, insomnia, sleep apnea and narcolepsy), withdrawal from abuse of drugs (such as of cocaine, ethanol, nicotine, benzodiazepines, alcohol, caffeine, phencyclidine and phencyclidine-like compounds, opiates such as cannabis, heroin, morphine, sedative ipnotic, amphetamine or amphetamine-related drugs such as dextroamphetamine, methylamphetamine or a combination thereof), motor disorders such as Parkinson's disease, dementia in Parkinson's disease, neuroleptic-induced Parkinsonism and tardive dyskinesias, as well as other psychiatric disorders, and certain gastrointestinal disorders such as irritable bowel syndrome.

It is to be understood that "treatment" as used herein includes prophylaxis as well as alleviation of established symptoms.

Thus the invention also provides a compound of formula (I) or a pharmaceutically acceptable salt thereof, for use as a therapeutic substance, in particular in the treatment of a CNS disorder such as depression (which term includes bipolar depression, unipolar depression, single or recurrent major depressive episodes with or without psychotic features, catatonic features, melancholic features, atypical features or postpartum onset, seasonal affective disorder and dysthymia, depressive disorders resulting from a general medical condition including, but not limited to, myocardial infarction, diabetes, miscarriage or abortion), anxiety disorders (which includes generalised anxiety and social anxiety disorder), schizophrenia, panic disorder, agoraphobia, social phobia, obsessive compulsive disorder, post-traumatic stress disorder, pain (particularly neuropathic pain), memory disorders (including dementia, amnesic disorders and age-associated memory impairment), disorders of eating behaviours (including anorexia nervosa and bulimia nervosa), sexual dysfunction, sleep disorders (including disturbances of circadian rhythm, dyssomnia, insomnia, sleep apnea and narcolepsy), withdrawal from abuse of drugs (such as of cocaine, ethanol, nicotine, benzodiazepines, alcohol, caffeine, phencyclidine and phencyclidine-like compounds, opiates such as cannabis, heroin, morphine, sedative ipnotic, amphetamine or amphetamine-related drugs such as dextroamphetamine, methylamphetamine or a combination thereof), motor disorders such as Parkinson's disease, dementia in Parkinson's disease, neuroleptic-induced Parkinsonism and tardive dyskinesias, as well as other psychiatric disorders, and certain gastrointestinal disorders such as irritable bowel syndrome.

In particular the invention provides a compound of formula (I) or a pharmaceutically acceptable salt thereof for use as a therapeutic substance in the treatment of depression and/or anxiety.

Compounds of the invention may be administered in combination with other active substances such as 5HT3 antagonists, serotonin agonists, NK-1 antagonists, selective serotonin reuptake inhibitors (SSRI), noradrenaline re-uptake inhibitors (SNRI), tricyclic antidepressants and/or dopaminergic antidepressants.

Suitable 5HT3 antagonists which may be used in combination of the compounds of the inventions include for example ondansetron, granisetron, metoclopramide.

Suitable serotonin agonists which may be used in combination with the compounds of the invention include sumatriptan, rauwolscine, yohimbine, metoclopramide.

Suitable SSRIs which may be used in combination with the compounds of the invention include fluoxetine, citalopram, femoxetine, fluvoxamine, paroxetine, indalpine, sertraline, zimeldine.

Suitable SNRIs which may be used in combination with the compounds of the invention include venlafaxine and reboxetine.

Suitable tricyclic antidepressants which may be used in combination with a compound of the invention include imipramine, amitriptiline, chlomipramine and nortriptiline.

Suitable dopaminergic antidepressants which may be used in combination with a compound of the invention include bupropion and amineptine.

It will be appreciated that the compounds of the combination or composition may be administered simultaneously (either in the same or different pharmaceutical formulations), separately or sequentially.

The invention further provides a method of treatment of the above disorders in mammals including humans, which comprises administering to the sufferer a therapeutically safe and effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

In another aspect, the invention provides for the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in the treatment of the above disorders.

In order to use the compounds of formula (I) in therapy, they will normally be formulated into a pharmaceutical composition in accordance with standard pharmaceutical practice. The present invention also provides a pharmaceutical composition, which comprises a compound of formula (I) or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or excipient.

In a further aspect, the present invention provides a process for preparing a pharmaceutical composition, the process comprising mixing a compound of formula (I) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or excipient.

A pharmaceutical composition of the invention, which may be prepared by admixture, suitably at ambient temperature and atmospheric pressure, is usually adapted for oral, parenteral or rectal administration and, as such, may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders, injectable or infusible solutions or suspensions or suppositories. Orally administrable compositions are generally preferred.

Tablets and capsules for oral administration may be in unit dose form, and may contain conventional excipients, such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose);, fillers (e.g. lactose, microcrystalline cellulose or calcium hydrogen phosphate);, tabletting lubricants lubricants (e.g. magnesium stearate, talc or silica);, disintegrants (e.g. potato starch or sodium starch glycollate); and acceptable wetting agents (e.g. sodium lauryl sulphate). The tablets may be coated according to methods well known in normal pharmaceutical practice.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspension, solutions, emulsions, syrups or elixirs, or may be in the form of a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents (e.g. sorbitol syrup, cellulose derivatives or hydrogenated edible fats), emulsifying agents (e.g. lecithin or acacia), non-aqueous vehicles (which may include edible oils e.g. almond oil, oily esters, ethyl alcohol or fractionated vegetable oils), preservatives (e.g. methyl or propyl-p-hydroxybenzoates or sorbic acid), and, if desired, conventional flavourings or colorants, buffer salts and sweetening agents as appropriate. Preparations for oral administration may be suitably formulated to give controlled release of the active compound.

For parenteral administration, fluid unit dosage forms are prepared utilising a compound of the invention or pharmaceutically acceptable salt thereof and a sterile vehicle. Formulations for injection may be presented in unit dosage form e.g. in ampoules or in multi-dose, utilising a compound of the invention or pharmaceutically acceptable salt thereof and a sterile vehicle, optionally with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use. The compound, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions, the compound can be dissolved for injection and filter sterilised before filling into a

suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. Parenteral suspensions are prepared in substantially the same manner, except that the compound is suspended in the vehicle instead of being dissolved, and sterilisation cannot be accomplished by filtration. The compound can be sterilised by exposure to ethylene oxide before suspension in a sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

Lotions may be formulated with an aqueous or oily base and will in general also contain one or more emulsifying agents, stabilising agents, dispersing agents, suspending agents, thickening agents, or colouring agents. Drops may be formulated with an aqueous or non-aqueous base also comprising one or more dispersing agents, stabilising agents, solubilising agents or suspending agents. They may also contain a preservative.

The compounds of the invention may also be formulated in rectal compositions such as suppositories or retention enemas, e.g. containing conventional suppository bases such as cocoa butter or other glycerides.

The compounds of the invention may also be formulated as depot preparations. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds of the invention may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

For intranasal administration, the compounds of the invention may be formulated as solutions for administration via a suitable metered or unitary dose device or alternatively as a powder mix with a suitable carrier for administration using a suitable delivery device. Thus compounds of formula (I) may be formulated for oral, buccal, parenteral, topical (including ophthalmic and nasal), depot or rectal administration or in a form suitable for administration by inhalation or insufflation (either through the mouth or nose).

The compounds of the invention may be formulated for topical administration in the form of ointments, creams, gels, lotions, pessaries, aerosols or drops (e.g. eye, ear or nose drops). Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Ointments for administration to the eye may be manufactured in a sterile manner using sterilised components.

The composition may contain from 0.1% to 99% by weight, preferably from 10 to 60% by weight, of the active material, depending on the method of administration. The dose of the compound used in the treatment of the aforementioned disorders will vary in the usual way

with the seriousness of the disorders, the weight of the sufferer, and other similar factors. However, as a general guide suitable unit doses may be 0.05 to 1000 mg, more suitably 1.0 to 200 mg, and such unit doses may be administered more than once a day, for example two or three times a day. Such therapy may extend for a number of weeks or months.

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

The following Preparations and Examples illustrate the compounds of the present invention and preparation thereof.

Description 1

2-Methyl-5-quinolinyl trifluoromethanesulfonate (D1)

A solution of 2-methyl-quinolin-5-ol (2.5 g; 1 eq) in dichloromethane (25 mL) and pyridine (6.4 mL; 5 eq) was cooled to 0°C and trifluoromethanesulfonic anhydride (4.2 mL; 1.6 eq) was added dropwise over 10 minutes. The reaction mixture was stirred under an inert atmosphere at r.t. for 1 h, then poured into water (20 mL) and extracted into ethyl acetate (3x15 mL). The organic layers were combined, dried over Na_2SO_4 and concentrated under reduced pressure. The crude was purified by flash chromatography, eluting with ethyl acetate/cyclohexane (4/6) affording the **title compound** in 92% yield (4.2 g).

MS; (ES) m/z: 292.3 [MH^+]. $C_{11}H_8F_3NO_3S$ requires 291.

1H-NMR (300 MHz, d_6-DMSO) δ(ppm): 8.05 (d, 1 H), 7.85 (d, 1 H), 7.64 (t, 1H), 7.48 (d, 1 H), 7.43 (d, 1 H), 2.48 (s, 3 H).

Description 2

1,1-Dimethylethyl 4-(2-methyl-5-quinolinyl)-1-piperazinecarboxylate (D2)

tert-Butyl 1-piperazine carboxylate (1.6 g; 1.2 eq), cesium carbonate (1.7 g; 1.5 eq), palladium acetate (0.33 g; 0.14 eq) and 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (0.97 mg; 0.15 eq) were added to a solution of 2-methyl-5-quinolinyl trifluoromethanesulfonate (**D1**) in toluene (20 mL) under an inert atmosphere. The reaction mixture was stirred at reflux under nitrogen for 8 hours. The reaction was quenched at room temperature using a saturated aqueous solution of ammonium chloride (15 mL) and extracted into ethyl acetate (3x20 mL). The organic layers were combined, dried over Na_2SO_4 and concentrated under reduced pressure. The crude was purified by flash chromatography, eluting with ethyl acetate/cyclohexane (3/7) affording the **title compound** in 62% yield (1.4 g).

MS; (ES) m/z: 328.4 [$MH]^+$. $C_{19}H_{25}N_3O_2$ requires 327.

^{1}H-NMR (500 MHz, $CDCl_3$) δ(ppm): 8.40 (d, 1 H), 7.76 (d, 1 H), 7.61 (t, 1 H), 7.29 (d, 1 H), 7.06 (d, 1 H), 3.69 (bs, 4 H), 3.03 (bs, 4 H), 2.74 (s, 3 H), 1.51 (s, 9 H).

Description 3

2-Methyl-5-(1-piperazinyl)quinoline (D3)

1,1-dimethylethyl 4-(2-methyl-5-quinolinyl)-1-piperazinecarboxylate (**D2**) (1.1 g) in a 25% solution of trifluoroacetic acid in dichloromethane (10 mL) was stirred at r.t. under an inert atmosphere for 3 hours. The reaction mixture was concentrated under reduced pressure and desalted by means of a 20g SCX cartridge affording the **title compound** in 96% yield (0.74 g).

MS; (ES) m/z: 228.4 $[MH]^+$. $C_{14}H_{17}N_3$ requires 227.

^{1}H-NMR (300 MHz, d_6-DMSO) δ(ppm): 8.34 (d, 1 H), 7.57 (m, 2 H), 7.35 (m, 1 H), 7.06 (m, 1 H), 2.93 (bm, 8 H), 2.62 (s, 3 H).

Description 4

2-(3-Nitrophenyl)ethyl methanesulfonate (D4)

Methanesulfonyl chloride (0.28 mL) was added dropwise to a stirred solution of 2-(3-nitrophenyl)ethanol (0.5 g; 1 eq) in dichloromethane (3 mL) and triethylamine (0.5 mL; 1.2 eq) at 0°C under an inert atmosphere. The solution was allowed to reach r.t. and stirred for 5 hours. The reaction mixture was diluted with water (3 mL) and extracted into dichloromethane (3x3 mL). The organic layers were combined, dried over Na_2SO_4 and concentrated under reduced pressure. The crude was purified by flash chromatography, eluting with a gradient from dichloromethane to dichloromethane/MeOH (98/2) affording the **title compound** in 84% yield (0.62 g).

^{1}H-NMR (300 MHz, $CDCl_3$) δ(ppm): 8.15 (m, 2 H), 7.53 (m, 2 H), 4.45 (t, 2 H), 3,15 (t, 2H), 2.92 (s, 3 H).

Description 5

2-Methyl-5-{4-[2-(3-nitrophenyl)ethyl]-1-piperazinyl}quinoline (D5)

N,N-Diisopropylethylamine (0.8 mL; 5 eq) was added to a solution of 2-methyl-5-(1-piperazinyl)quinoline (**D3**) (0.2 g; 1 eq) and 2-(3-nitrophenyl)ethyl methanesulfonate (**D4**) (0.22; 1 eq) in dimethylformamide (1.5 mL). The reaction mixture was heated to 100°C for 10 hours. The dark solution was concentrated under reduced pressure, diluted with water (3 mL) and brine (1mL) and extracted into ethyl acetate (3x3 mL). The organic layers were combined, dried over Na_2SO_4 and concentrated under reduced pressure. The crude was purified by flash chromatography, eluting with a gradient from dichloromethane to dichloromethane/MeOH (98/2) affording the **title compound** in 64% yield (0.21 g).

MS; (ES) m/z: 228.4 $[MH]^+$. $C_{22}H_{24}N_4O_2$ requires 376.

^{1}H-NMR (300 MHz, $CDCl_3$) δ(ppm): 8.35 (d, 1 H), 8.11 (s, 1 H), 8.05 (d, 1 H), 7.70 (d, 1 H), 7.55 (m, 2 H), 7.45 (t, 1 H), 7.25 (m, 1 H), 7.05 (d, 1 H), 3.10 (mt, 4 H), 2.95 (bm, 2 H), 2.75 (bm, 6 H), 2.70 (s, 3 H).

Description 6

3-{2-[4-(2-Methyl-5-quinolinyl)-1-piperazinyl]ethyl}aniline (D6)

A solution of 2-methyl-5-{4-[2-(3-nitrophenyl)ethyl]-1-piperazinyl}quinoline (**D5**)(0.14 g; 1 eq) in methanol (3 mL) was added dropwise to a suspension of iron powder (0.07 g; 3.2 eq) and

ammonium chloride (0.1 g; 5.3 eq) in water (3 mL). The reactants were heated at reflux for 8 hours, adding additional amounts of iron powder (total 0.07g; 3.2 eq) and ammonium chloride (total 0.1g; 5.03 eq) in 3 portions during the reaction. The reaction mixture was filtered using a Millipore filter. The filtrate was concentrated under reduced pressure, diluted with water (5 mL) and a saturated aqueous solution of sodium hydrogen carbonate (2 mL), extracted into ethyl acetate (3x5 mL), dried over Na_2SO_4 and concentrated under reduced pressure obtaining the **title compound** in 84% yield (0.11 g).
MS; (ES) m/z: 347.4 $[MH]^+$. $C_{22}H_{26}N_4$ requires 346.
^{1}H-NMR (300 MHz, $CDCl_3$) δ(ppm): 8.35 (d, 1 H), 7.70 (d, 1 H), 7.55 (t, 1 H), 7.25 (d, 1 H), 7.08 (m, 2 H), 6.65 (md, 1 H), 6.55 (m, 2 H), 3.65 (bs, 2 H), 3.15 (t, 4 H), 2.80 (m, 4 H), 2.75 (s, 3 H), 2.70 (m, 4 H).

Description 7

***N*-Methyl-3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}aniline (D7)**

Propyl (3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}phenyl)carbamate dihydrochloride (**E47**) (0.065 mmol) was charged onto an SPE cartridge (SCX) and eluted with a solution of ammonia in MeOH to obtain the corresponding free base (0.0618 mmol). This was then dissolved in tetrahydrofuran (1 ml) and treated with $LiAlH_4$ (3 equiv.). The resulting reaction mixture was warmed to 70 °C and stirred for 3 h. Then, the reaction mixture was poured into NH_4Cl aq. at 0 °C. The aqueous phase was extracted with dichloromethane (20 ml). The organic phases were washed with water, dried over Na_2SO_4 and concentrated under reduced pressure. The crude was purified on SPE cartridge (Silica) using CH_2Cl_2/MeOH (98/2) as eluent to give the **title compound** in 43% yield.
MS: (ES/+) m/z: 361 $[MH^+]$. $C_{23}H_{28}N_4$ required 360.
^{1}H-NMR (300 MHz, $CDCl_3$) δ(ppm): 8.35 (1H, d), 7.70 (1H, d), 7.65 (1H, t), 7.15-7.00 (2H, m), 6.55 (1H, d), 6.50-6.40 (2H, m) 3.15 (4H, m), 2.85-2.65 (8H, m), 2.80 (3H, s), 2.70 (3H, s).

Description 8

1-(3-Aminophenyl)-2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethanol (D8)

Sodium carbonate (1.5 eq) and 2-bromo-1-(3-nitrophenyl)ethanone (1.5 eq) were added to a stirred solution of 2-methyl-5-(1-piperazinyl)quinoline (**D3**) (1 eq) in tetrahydrofuran at room temperature under an inert atmosphere, and the reaction was left under stirring for 1h. The solution was then diluted with MeOH, $NaBH_4$ (2 eq) was added and the reaction was left under stirring for 1h. The solvent was removed under reduced pressure.
The crude material was purified on SPE cartridge (SCX) using as eluant a gradient from MeOH to MeOH:CH_2Cl_2 (1:1) and then 2M NH_3 in MeOH affording an intermediate which was reduced following a similar procedure to **D6** to give the title compound in 55% yield.
MS: (ES/+) m/z: 363 $[MH^+]$. $C_{22}H_{26}N_4O$ required 362.
^{1}H-NMR (300 MHz, $CDCl_3$) δ(ppm): 8.35 (1H, d), 7.70 (1H, d), 7.55 (1H, t), 7.25 (1H, d), 7.10 (1H, t), 7.05 (1H, d), 6.80-6.70 (2H, m), 6.60 (1H, dd), 4.70 (1H, dd), 3.65 (2H, bs), 3.15 (4H, bs), 3.00 (2H, bm), 2.80-2.50 (7H, m).

General procedure for the preparation of amides, ureas and carbamates starting from arylbromides: Method A

K_2CO_3 (1.5eq), an amide, urea or carbamate (2 eq), CuI (0.1 eq) and *N,N'*-dimethyl-1,2-ethanediamine (0.11 eq) were added to a stirred solution of an arylbromide (1 eq) in dioxane at room temperature under an inert atmosphere, and the reaction was heated at 90-100 °C for 1-5 hrs. The mixture was then added to a saturated aqueous solution of NH_4Cl, and extracted with dichloromethane. The organic phase was washed with brine, dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude material was purified on SPE cartridge (Silica) using as eluant Cyclohexane/ethyl acetate 8:2, affording the final compound (yields ranged from 18 to 99%).

Description 9

1-(3-Acetylphenyl)-2-pyrrolidinone (D9)

The **title compound** was prepared in 98% yield according to the general procedure for the preparation of the amides, ureas and carbamates (Method A) starting from 1-(3-bromophenyl)ethanone and 2-pyrrolidinone.

MS: (ES) m/z: 204 [MH^+]. $C_{12}H_{13}NO_2$ requires 203.

^{1}H-NMR (300 MHz, $CDCl_3$) δ(ppm): 8.15 (bs, 1H), 8.0 (dd, 1H), 7.7 (dd, 1H), 7.45 (t, 1H), 3.95 (t, 2H), 2.65(m, 2H), 2.60 (s, 3H), 2.2 (m, 2H).

Description 10

1-(3-Acetylphenyl)-2-azetidinone (D10)

The **title compound** was prepared in 97% yield according to the general procedure for the preparation of the amides, ureas and carbamates (Method A) starting from 1-(3-bromophenyl)ethanone and 2-azetidinone.

MS: (ES) m/z: 190 [MH^+]. $C_{11}H_{11}NO_2$ requires 189.

^{1}H-NMR (300 MHz, $CDCl_3$) δ(ppm): 7.6 (d, 1H); 7.55(dd, 1H); 7.45(dd, 1H); 7.2 (t, 1H); 3.5 (t, 2H), 3.0 (t.2H), 2.45 (s, 3H)

Description 11

3-(3-Acetylphenyl)-1,3-oxazolidin-2-one (D11)

The **title compound** was prepared in quantitative yield according to the general procedure for the preparation of the amides, ureas and carbamates (Method A) starting from 1-(3-bromophenyl)ethanone and 1,3-oxazolidin-2-one.

MS: (ES) m/z: 206 [MH^+]. $C_{11}H_{11}NO_3$ requires 205.

^{1}H-NMR (300 MHz, $CDCl_3$) δ(ppm): 7.95 (m, 2H), 7.7 (dd, 1H), 7.45 (t, 1H), 4.5 (t, 2H), 4.2 (t, 2H), 2.6 (s, 3H)

Description 12

1-(3-Acetylphenyl)-2-imidazolidinone (D12)

The **title compound** was prepared in 18% yield according to the general procedure for the preparation of the amides, ureas and carbamates (Method A) starting from 1-(3-bromophenyl)ethanone and 2-imidazolidinone.
MS: (ES) m/z: 205 [MH^+]. $C_{11}H_{12}N_2O_2$ requires 204.
^{1}H-NMR (300 MHz, $CDCl_3$) δ(ppm): 7.8 (m, 2H), 7.54 (dd, 1H), 7.25 (t, 1H), 5.0 (bs, 1H), 3.8 (t, 2H), 3.4 (t, 2H), 2.45 (s, 3H).

Description 13
2-(3-Bromophenyl)ethyl methanesulfonate (D13)
The **title compound** was prepared in XX% yield using a similar procedure to description **D4** starting from 2-(3-bromophenyl)ethanol.
MS: (ES/+) m/z: 278 and 280 [MH^+]. $C_9H_{11}BrO_3S$ requires 277 and 279.
^{1}H-NMR (200 MHz, $CDCl_3$) δ(ppm): 7.40(2H, m), 7.5 (2H, m), 4.40 (2H, t), 3.00 (2H, t), 2.85 (3H, s).

Description 14
5-{4-[2-(3-Bromophenyl)ethyl]-1-piperazinyl}-2-methylquinoline (D14)
The **title compound** was prepared in 56% yield using a similar procedure to description **D5** starting from 2-methyl-5-(1-piperazinyl)quinoline (**D3**) and 2-(3-bromophenyl)ethyl methanesulfonate (**D13**).
MS: (ES/+): m/z: 412 and 410 [MH^+]. $C_{22}H_{24}BrN_3$ requires 409 and 411.
^{1}H-NMR (400 MHz, $CDCl_3$) δ(ppm): 8.29 (1H, d), 7.54 (2H, m),7.35 (1H, br m), 7.34 (1H, d), 7.23 (2H, m), 7.06 (1H, dd), 2.98 (4H, br s), 2.76 (2H, br t), 2.68 (5H, br s), 2.59 (2H, br m), 2.58 (3H, s).

Description 15
2-(3-Nitrophenyl)ethyl 4-nitrobenzenesulfonate (D15)
The **title compound** was prepared in 68% yield using a similar procedure to description **D4** starting from 2-(3-nitro-phenyl)ethanol and 4-nitrobenzenesulfonyl chloride.
MS: (ES) m/z: 351 [MH^+]. $C_{14}H_{12}N_2O_7S$ requires 352.
^{1}H-NMR (300 MHz, $CDCl_3$) δ(ppm): 8.3 (m, 2H), 8.05 (d, 1H), 8.0-7.9 (m, 3H), 7.5 (m, 2H), 4.4 (t, 2H), 3.1 (t, 2H).

Description 16
7-Chloro-2-methyl-5-(1-piperazinyl)quinoline (D16)
The **title compound** was prepared from 7-chloro-5-hydroxy-2-methylquinoline (WO/0234754) using similar procedures to descriptions **D1**, **D2** and **D3**.
MS; (ES) m/z: 262.1 [$MH]^+$. $C_{14}H_{16}ClN_3$ requires 261.
^{1}H-NMR (300 MHz, d_6-DMSO) δ(ppm): 8.36 (d, 1 H), 7.61 (d, 1 H), 7.40 (d, 1 H), 6.92 (d, 1 H , 3.32 (m, 4 H), 2.93 (m, 4 H), 2.62 (s, 3 H).

Description 17

7-Chloro-2-methyl-5-{4-[2-(3-nitrophenyl)ethyl]-1-piperazinyl}quinoline (D17)
The **title compound** was prepared in 92% yield using a similar procedure to description **D5** starting from 7-chloro-2-methyl-5-(1-piperazinyl)quinoline (**D16**) and 2-(3-Nitrophenyl)ethyl 4-nitrobenzenesulfonate (**D15**).
MS: (ES) m/z: 411 [MH^+]. $C_{22}H_{23}ClN_4O_2$ requires 410.
^{1}H-NMR (300 MHz, $CDCl_3$) δ(ppm): 8.3 (d, 1H), 8.2 (bd, 1H), 8.05 (bd, 1H), 7.7 (s, 1H), 7.55 (d, 1H), 7.4 (t, 1H), 7.2 (d, 1H), 6.95 (s, 1H), 3.1 (bm, 4H), 2.95 (t, 2H), 2.8-2.6 (bm, 6H), 2.6 (s, 3H)

Description 18
3-{2-[4-(7-Chloro-2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}aniline (D18)
The **title compound** was prepared in 92% yield using a similar procedure to description **D6** starting from 7-Chloro-2-methyl-5-{4-[2-(3-nitrophenyl)ethyl]-1-piperazinyl}quinoline (**D17**).
MS: (ES) m/z: 381 [MH^+]. $C_{22}H_{25}ClN_4$ requires 380.
^{1}H-NMR (300 MHz, $CDCl_3$) δ(ppm): 8.25 (d, 1H), 7.65 (s, 1H), 7.2 (d, 1H), 7.05 (t, 1H), 6.95 (s, 1H), 6.6 (d, 1H), 6.5 (m, 2H), 3.6 (bs, 2H), 2.8-2.5 (m, 12H), 2.65 (s, 3H)

Description 19
[3-(1*H*-Pyrazol-1-yl)phenyl]acetic acid (D19)
Pyrazole (1.2 eq), Cs_2CO_3 (2.5 eq), CuI (0.5 eq), *trans*-1,2-cyclohexanediamine (0.6 eq) and dodecane (1 eq), were added to a stirred solution of 3-bromophenylacetic acid (1 eq) in dioxane at room temperature under an inert atmosphere. The mixture was irradiated in a microwave reactor (PersonalChemistry Emrys™ Optimiser, 300W, 160 °C, 20 min), then added to a 1N aqueous solution of NaOH, and extracted with Et_2O. The aqueous phase was acidified to pH=3 with HCl 2N, then extracted with ethyl acetate; this phase was washed with brine, dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude material was purified on SPE cartridge (Silica) eluting with a gradient from Cyclohexane/ethyl acetate 8:2, to Cyclohexane/ethyl acetate 1:1, affording the **title compound** in 65% yield.
MS: (ES) m/z: 203 [MH^+]. $C_{11}H_{10}N_2O_2$ requires 202.
^{1}H-NMR (300 MHz, $CDCl_3$) δ(ppm): 7.9 (m, 1H), 7.75 (m, 1H), 7.65 (m, 1H), 7.55 (d, 1H), 7.35 (t, 1H), 7.3-7.1 (m, 2H), 6.55 (m, 1H), 3.7 (s, 2H)

Examples

General procedure for the preparation of amides starting from 3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}aniline (D6): Method B
Triethylamine or diisopropylethylamine (1.7eq) and then an acyl chloride (1.5 eq) were added dropwise to a stirred solution of 3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}aniline (**D6**) (1 eq) in dichloromethane at room temperature under an inert atmosphere. The reaction was left under stirring for 16 h. The mixture was then washed with

a saturated aqueous solution of NH_4Cl, a saturated aqueous solution of $NaHCO_3$, brine, dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude material was purified on SPE cartridge (Silica) using as eluent a gradient from dichloromethane/MeOH 99/1 to dichloromethane/MeOH 98/2 affording the final compound (yields ranged from 30 to 80%).

General procedure for the preparation of amides and their corresponding dihydrochloride salts starting from 3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl] ethyl}aniline (D6): Method C

EDC•HCl (1.5 eq) and HOBt (1.5eq) were added sequentially to a stirred solution of a carboxylic acid (1.5 eq) in dichloromethane/dimethylformamide (1/1) at room temperature. The reaction mixture was left under stirring for 30 min then 3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}aniline (**D6**) (1eq) dissolved in dichloromethane/dimethylformamide (1/1) was added dropwise. The solution was stirred for 16 h then diluted with dichloromethane and washed with a saturated aqueous solution of $NaHCO_3$ and brine and then dried over Na_2SO_4. The solution was concentrated under reduced pressure and the residual solvent was removed by means of an SCX cartridge. The crude material was purified on SPE cartridge (Silica) eluting from a gradient from dichloromethane/MeOH 99/1 to dichloromethane/MeOH 98/2 affording the final compound (yields ranged from 20 to 96%).
The free base could be converted into its dihydrochloride salt by dissolving the compound in dichloromethane and adding a 1M ethereal solution of HCl (2.1 eq) dropwise. A yellow solid precipitated and the suspension was stirred for 15 min. The solvent was removed under reduced pressure affording a crude material which was triturated with Et_2O. The final compound was then recovered by filtration (yield quantitative).

Example 1
***N*-(3-{2-[4-(2-Methyl-5-quinolinyl)-1-piperazinyl]ethyl}phenyl)acetamide (E1)**
The **title compound** was prepared in 52% yield according to the general procedure for the preparation of the amides (Method B) starting from 3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}aniline (**D6**) and acetyl chloride.
MS; (ES) m/z: 389 $[MH]^+$. $C_{24}H_{28}N_4O$ requires 388.
^{1}H-NMR (500 MHz, d_6-DMSO) δ(ppm): 9.84 (s, 1 H), 8.33 (d, 1 H), 7.58 (m, 2 H), 7.46 (s, 1 H), 7.39 (m, 2 H), 7.19 (t, 1 H), 7.10 (dd, 1 H), 6.92 (d, 1 H), 3.03 (bm, 4 H), 2.73 (bm, 6 H), 2.62 (s+bm, 5 H), 2.02 (s, 3 H).

Example 2
***N*-(3-{2-[4-(2-Methyl-5-quinolinyl)-1-piperazinyl]ethyl}phenyl)propanamide (E2)**
The **title compound** was prepared in 73% yield according to the general procedure for the preparation of the amides (Method B) starting from 3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}aniline (**D6**) and propanoyl chloride.

MS: (ES/+) m/z: 403 [MH^+]. $C_{25}H_{30}N_4O$ requires 402.
^{1}H-NMR (300 MHz, $CDCl_3$) δ(ppm): 8.35 (d, 1H), 7.70 (d, 1H), 7.55 (t, 1H), 7.50 (br s, 1H), 7.25 (m, 3H), 7.12 (br, 1H), 7.07 (d, 1H), 6.98 (br d, 1H), 3.20 (br m, 4H), 3.00-2.75 (br m, 8H), 2.73 (s, 3H), 2.37 (q, 2H), 1.23 (t, 3H)

Example 3

2-Methyl-*N*-(3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}phenyl) propanamide (E3)

The **title compound** was prepared in 81% yield according to the general procedure for the preparation of the amides (Method B) starting from 3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}aniline (**D6**) and 2-methylpropanoyl chloride.
MS: (ES/+) m/z: 417 [MH^+]. $C_{28}H_{32}N_4O$ requires 416.
^{1}H-NMR (300 MHz, $CDCl_3$) δ(ppm): 8.35 (d, 1H), 7.70 (d, 1 H), 7.55 (m, 2H), 7.25 (m, 3H), 7.13 (br s, 1H), 7.08 (d, 1H), 6.98 (br d, 1H), 3.20 (br m, 4H), 3.00-2.75 (br m, 8 H), 2.73 (s, 3H), 2.48 (m, 1H), 1.25 (d, 6H)

Example 4

3-Methyl-*N*-(3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}phenyl) butanamide (E4)

The **title compound** was prepared in 64% yield according to the general procedure for the preparation of the amides (Method B) starting from 3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}aniline (**D6**) and 3-methylbutanoyl chloride.
MS: (ES/+) m/z: 431 [MH^+]. $C_{27}H_{34}N_4O$ requires 430.
^{1}H-NMR (300 MHz, $CDCl_3$) δ(ppm): 8.35 (d, 1H), 7.70 (d, 1H), 7.60-7.50 (m, 2H), 7.30-7.20 (m, 3H), 7.10 (d, 2H), 7.00 (d, 1H), 3.20 (br s, 4H), 3.00-2.80 (br m, 8H), 2.70 (s , 3H), 2.20 (m, 3H), 1.00 (d, 6H).

Example 5

2,2-Dimethyl-*N*-(3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}phenyl) propanamide (E5)

The **title compound** was prepared in 66% yield according to the general procedure for the preparation of the amides (Method B) starting from 3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}aniline (**D6**) and 2,2-dimethylpropanoyl chloride.
MS: (ES/+) m/z: 431 [MH^+]. $C_{27}H_{34}N_4O$ requires 430.
^{1}H-NMR (300 MHz, $CDCl_3$) δ(ppm): 8.35 (d, 1H), 7.70 (d, 1H), 7.55 (t, 2H), 7.30-7.20 (m, 4H), 7.10 (d, 1H), 7.00 (m, 1H), 3.20 (br s, 4H), 2.85 (br s, 8H), 2.70 (s , 3H), 1.30 (s, 9H)

Example 6

***N*-(3-{2-[4-(2-Methyl-5-quinolinyl)-1-piperazinyl]ethyl}phenyl)benzamide (E6)**

The **title compound** was prepared in 60% yield according to the general procedure for the preparation of the amides (Method B) starting from 3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}aniline (**D6**) and benzoyl chloride.
MS: (ES/+) m/z: 451 [MH^+]. $C_{29}H_{30}N_4O$ requires 450.

^{1}H-NMR (300 MHz, $CDCl_3$) δ(ppm): 8.35 (d, 1H), 7.87 (m, 2H), 7.80 (br s, 1H), 7.72 (d, 1H), 7.65 (br s, 1H), 7.6-7.4 (m, 5H), 7.30 (t, 1H), 7.27 (m, 1H), 7.08 (d, 1H), 7.05 (d, 1H), 3.18 (br s, 4H), 3.00-2.75 (br m, 8H), 2.72 (s , 3H).

Example 7

***N*-(3-{2-[4-(2-Methyl-5-quinolinyl)-1-piperazinyl]ethyl}phenyl)-2-phenyl acetamide (E7)**

The **title compound** was prepared in 64% yield according to the general procedure for the preparation of the amides (Method B) starting from 3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}aniline (**D6**) and phenylacetyl chloride.

MS: (ES/+) m/z: 465 [MH^+]. $C_{30}H_{32}N_4O$ requires 464.

^{1}H-NMR (300 MHz, $CDCl_3$) δ(ppm): 8.35 (d, 1H), 7.70 (d, 1H), 7.55 (t, 1H), 7.45-7.15 (m, 9H), 7.10-6.95 (m, 3H), 3.70 (s, 2H), 3.10 (br s, 4H), 2.90-2.70 (br s , 8H), 2.70 (s, 3H).

Example 8

3,3-Dimethyl-*N*-(3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}phenyl) butanamide (E8)

The **title compound** was prepared in 62% yield according to the general procedure for the preparation of the amides (Method B) starting from 3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}aniline (**D6**) and 3,3-dimethylbutanoyl chloride.

MS: (ES/+) m/z: 445 [MH^+]. $C_{28}H_{36}N_4O$ requires 444.

^{1}H-NMR (300 MHz, $CDCl_3$) δ(ppm): 8.35 (d, 1H), 7.70 (d, 1H), 7.60-7.45 (m, 2H), 7.30-7.20 (m, 3H), 7.15-7.05 (m, 2H), 7.00 (d, 1H), 3.10 (t, 4H), 2.90-2.60 (m , 8H), 2.65 (s, 3H), 2.20 (s, 2H), 1.05 (s, 9H).

Example 9

***N*-(3-{2-[4-(2-Methyl-5-quinolinyl)-1-piperazinyl]ethyl}phenyl)cyclohexane carboxamide (E9)**

The **title compound** was prepared in 30% yield according to the general procedure for the preparation of the amides (Method B) starting from 3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}aniline (**D6**) and cyclohexanecarbonyl chloride.

MS: (ES/+) m/z: 457 [MH^+]. $C_{29}H_{36}N_4O$ requires 456.

^{1}H-NMR (300 MHz, $CDCl_3$) δ(ppm): 8.35 (d, 1H), 7.70 (d, 1H), 7.60-7.50 (m, 2H), 7.30-7.20 (m, 3H), 7.15-7.05 (m, 2H), 7.00 (d, 1H), 3.15 (br s, 4H), 2.95-2.75 (m , 8 H), 2.70 (s, 3H), 2.20-1.40 (m, 7H), 1.40-1.10 (m, 4 H).

Example 10

5-Methyl-*N*-(3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}phenyl)-3-isoxazolecarboxamide (E10)

The **title compound** was prepared in 40% yield according to the general procedure for the preparation of the amides (Method B) starting from 3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}aniline (**D6**) and 5-methyl-3-isoxazolecarbonyl chloride.

MS: (ES/+) m/z: 456 [MH^+]. $C_{27}H_{29}N_5O2$ requires 455.

^{1}H-NMR (300 MHz, $CDCl_3$) δ(ppm): 8.50 (s, 1H), 8.35 (d, 1H), 7.70 (d, 1H), 7.60 (m, 2 H), 7.40 (d, 1H), 7.30-7.20 (m, 2H), 7.20-7.10 (t, 2H), 6.50 (s, 1H), 3.15 (t, 4H), 2.95-2.70 (m , 8H), 2.70 (s, 3H), 2.50 (s, 3H).

Example 11

***N*-(3-{2-[4-(2-Methyl-5-quinolinyl)-1-piperazinyl]ethyl}phenyl)-2-(2-thienyl) acetamide (E11)**

The **title compound** was prepared in 42% yield according to the general procedure for the preparation of the amides (Method B) starting from 3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}aniline (**D6**) and 2-thienylacetyl chloride.

MS: (ES/+) m/z: 471 [MH^+]. $C_{28}H_{30}N_4OS$ requires 470.

^{1}H-NMR (300 MHz, $CDCl_3$) δ(ppm): 8.35 (d, 1H), 7.70 (d, 1H), 7.60 (t, 1H), 7.40 (s, 1H), 7.30 (dd, 1H), 7.25-7.15 (m, 3H), 7.10-6.90 (m, 5H), 3.90 (s, 2H), 3.15 (br s, 4H), 3.00-2.70 (m, 8H), 2.70 (s, 3H).

Example 12

2-(Methyloxy)-*N*-(3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}phenyl) acetamide (E12)

The **title compound** was prepared in 62% yield according to the general procedure for the preparation of the amides (Method B) starting from 3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}aniline (**D6**) and (methyloxy)acetyl chloride.

MS: (ES/+) m/z: 419 [MH^+]. $C_{25}H_{30}N_4O_2$ requires 418.

^{1}H-NMR (300 MHz, $CDCl_3$) δ(ppm): 8.35 (d, 1H), 8.20 (s, 1H), 7.70 (d, 1H), 7.60 (t, 1H), 7.50 (s, 1H), 7.35 (d, 1H), 7.30-7.20 (m, 2H), 7.10-6.90 (dd, 2H), 4.00 (s, 2H), 3.50 (s , 3H), 3.10 (t, 4H), 2.90-2.70 (m, 8H), 2.70 (s, 3H).

Example 13

***N*-(3-{2-[4-(2-Methyl-5-quinolinyl)-1-piperazinyl]ethyl}phenyl)-2-(phenyloxy) acetamide (E13)**

The **title compound** was prepared in 41% yield according to the general procedure for the preparation of the amides (Method B) starting from 3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}aniline (**D6**) and (phenyloxy)acetyl chloride.

MS: (ES/+) m/z: 481 [MH^+]. $C_{30}H_{32}N_4O_2$ requires 480.

^{1}H-NMR (400 MHz, $CDCl_3$) δ(ppm): 8.33 (d, 1H), 7.53 (m, 3H), 7.54 (br s, 1H), 7.46 (br d, 1H), 7.37 (d, 1H), 7.30 (dd, 2H), 7.23 (t, 1H), 7.09 (dd, 1H), 6.99 (m, 3H), 6.96 (t, 1H), 4.67 (s, 2H), 3.02 (br m, 4H), 2.80-2.60 (m, 8H), 2.62 (s, 3H).

Example 14

***N*-(3-{2-[4-(2-Methyl-5-quinolinyl)-1-piperazinyl]ethyl}phenyl)cyclopropane carboxamide (E14)**

The **title compound** was prepared in 70% yield according to the general procedure for the preparation of the amides (Method B) starting from 3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}aniline (**D6**) and cyclopropanecarbonyl chloride.
MS: (ES/+) m/z: 415 [MH^+]. $C_{26}H_{30}N_4O$ requires 414.
^{1}H-NMR (300 MHz, $CDCl_3$) δ(ppm): 8.35 (d, 1H), 7.60-7.50 (m, 2H), 7.30 (br s, 1H), 7.30-7.20 (m, 3H), 7.05 (d, 1H), 6.95 (br d, 1H), 3.10 (t, 4H), 2.90-2.70 (m, 8H), 2.70 (s, 3H), 1.20 (t, 1H), 1.10 (m, 2H), 0.85 (m, 2H).

Example 15
***N*-(3-{2-[4-(2-Methyl-5-quinolinyl)-1-piperazinyl]ethyl}phenyl)-2-oxo-4-imidazolidinecarboxamide (E15)**
The **title compound** was prepared in 51% yield according to the general procedure for the preparation of the amides (Method C) starting from 3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}aniline (**D6**) and 2-oxo-4-imidazolidinecarboxylic acid.
MS: (ES/+) m/z: 459 [MH^+]. $C_{26}H_{30}N_6O_2$ requires 458.
^{1}H-NMR (300 MHz, $CDCl_3$) δ(ppm): 8.40 (s, 1H), 8.38(d, 1H), 7.70 (d. 1H), 7.55 (t, 1H), 7.50 (d, 1H), 7.40 (dd, 1H), 7.30-7.20 (m, 2H), 7.05 (m, 2H), 5.20 (d, 1H), 4.75 (s, 1H), 4.45 (m, 1H), 4.00 (t, 1H), 3.65 (dd, 1H), 3.10 (br s, 4H), 2.95-2.70 (m, 8H), 2.70 (br s, 3H).

Example 16
***N*-(3-{2-[4-(2-Methyl-5-quinolinyl)-1-piperazinyl]ethyl}phenyl)-2-pyrazine carboxamide (E16)**
The **title compound** was prepared in 89% yield according to the general procedure for the preparation of the amides (Method C) starting from 3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}aniline (**D6**) and 2-pyrazinecarboxylic acid.
MS: (ES/+) m/z: 453 [MH^+]. $C_{27}H_{28}N_6O$ requires 452.
^{1}H-NMR (300 MHz, $CDCl_3$) δ(ppm): 9.65 (s, 1H), 9.50 (m, 1H), 8.80 (d, 1H), 8.60 (t, 1H) 8.38 (d, 1H), 7.75 (d, 1H), 7.70 (d, 1H), 7.58 (t, 1H), 7.55 (dd, 1H), 7.35 (t, 1H), 7.28 (d, 1H), 7.08 (m, 2H), 3.15 (br s, 4H) 2.95-2.70 (m, 8H), 2.70 (br s, 3H).

Example 17
5-(Methyloxy)-*N*-(3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}phenyl)-1,3-oxazole-2-carboxamide (E17)
The **title compound** was prepared in 30% yield according to the general procedure for the preparation of the amides (Method C) starting from 3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}aniline (**D6**) and 5-(methyloxy)-1,3-oxazole-2-carboxylic acid.
MS: (ES/+) m/z: 472 [MH^+]. $C_{27}H_{29}N_5O_2$ requires 471.
^{1}H-NMR (300 MHz, $CDCl_3$) δ(ppm): 8.58 (s, 1H), 8.39 (d, 1H), 7.71 (d, 1H), 7.58 (t, 1H) 7.60 (d, 1H), 7.48 (dd, 1H), 7.30 (t, 1H), 7.26 (d, 1H), 7.08 (dd, 1H), 7.04 (d, 1H), 6.28 (s, 1H), 4.03 (s, 3H), 3.15 (t, 4H) 2.95-2.70 (m, 8H), 2.74 (br s, 3H).

Example 18

***N*-(3-{2-[4-(2-Methyl-5-quinolinyl)-1-piperazinyl]ethyl}phenyl)-1,2,3-thiadiazole-4-carboxamide (E18)**

The **title compound** was prepared in 75% yield according to the general procedure for the preparation of the amides (Method C) starting from 3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}aniline (**D6**) and 1,2,3-thiadiazole-4-carboxylic acid.

MS: (ES/+) m/z: 459 [MH^+]. $C_{25}H_{26}N_6OS$ requires 458.

^{1}H-NMR (300 MHz, $CDCl_3$) δ(ppm): 9.30 (s, 1H), 9.25 (s, 1H), 8.38 (d, 1H), 7.70 (d, 1H), 7.68 (d, 1H) 7.58 (t, 1H), 7.55 (dd, 1H), 7.35 (t, 1H), 7.28 (d, 1H), 7.10 (m, 2H), 3.15 (br s, 4H) 2.95-2.70 (m, 8H), 2.70 (s, 3H).

Example 19

2,4-Dimethyl-*N*-(3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}phenyl)-1,3-thiazole-5-carboxamide (E19)

The **title compound** was prepared in 68% yield according to the general procedure for the preparation of the amides (Method C) starting from 3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}aniline (**D6**) and 2,4-dimethyl-1,3-thiazole-5-carboxylic acid.

MS: (ES/+) m/z: 486 [MH^+]. $C_{28}H_{31}N_5OS$ requires 485.

^{1}H-NMR (300 MHz, $CDCl_3$) δ(ppm): 8.38 (d, 1H), 7.70 (d, 1H), 7.58 (t, 1H) 7.55 (d, 1H), 7.35-7.20 (dd, 1H), 7.30 (br s, 1H), 7.10 (m, 2H), 3.15 (t, 4H) 2.95-2.70 (m, 8H), 2.72 (s, 6H), 2.70 (s, 3H).

Example 20

1,5-Dimethyl-*N*-(3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}phenyl)-1*H*-pyrazole-3-carboxamide (E20)

The **title compound** was prepared in 35% yield according to the general procedure for the preparation of the amides (Method C) starting from 3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}aniline (**D6**) and 1,5-dimethyl-1*H*-pyrazole-3-carboxylic acid.

MS: (ES/+) m/z: 469 [MH^+]. $C_{28}H_{32}N_6O$ requires 468.

^{1}H-NMR (300 MHz, $CDCl_3$) δ(ppm): 8.60 (s, 1H), 8.38 (d, 1H), 7.70 (d, 1H), 7.68 (d, 1H), 7.58 (t, 1H) 7.45 (d, 1H), 7.35-7.20 (dd, 2H), 7.08 (d, 1H), 7.00 (d,1H), 6.60 (s, 1H), 3.80 (s, 3H), 3.15 (t, 4H) 2.95-2.70 (m, 8H), 2.72 (s, 3H), 2.30 (s, 3H).

Example 21

***N*-(3-{2-[4-(2-Methyl-5-quinolinyl)-1-piperazinyl]ethyl}phenyl)-4-oxo-4,5,6,7-tetrahydro-1-benzofuran-2-carboxamide (E21)**

The **title compound** was prepared in 20% yield according to the general procedure for the preparation of the amides (Method C) starting from 3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}aniline (**D6**) and 4-oxo-4,5,6,7-tetrahydro-1-benzofuran-3-carboxylic acid.

MS: (ES/+) m/z: 509 [MH^+]. $C_{31}H_{32}N_4O_3$ requires 508.

^{1}H-NMR (300 MHz, $CDCl_3$) δ(ppm): 11.80 (s, 1H), 8.10 (s, 1H), 8.38 (d, 1H), 7.72 (d, 1H) 7.70 (d, 1H), 7.65 (dd, 1H), 7.58 (t, 1H), 7.30-7.20 (m, 2H), 7.08 (d, 1H), 7.00 (d, 1H), 3.15 (t, 4H), 3.00-2.65 (m, 12H), 2.70 (s, 3H), 2.25 (m, 2 H).

Example 22

2-Fluoro-*N*-(3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}phenyl) benzamide dihydrochloride salt (E22)

The **title compound** was prepared in 96% yield according to the general procedure for the preparation of the amides (Method C) starting from 3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}aniline (**D6**) and 2-fluorobenzoic acid.

MS: (ES/+) m/z: 469 [MH^+]. $C_{29}H_{28}FN_4O$ requires 468.

^{1}H-NMR (500 MHz, d_6-DMSO) δ(ppm): 11.00 (br s, 1H), 10.46 (s. 1H), 8.80 (br s, 1H), 8.00-7.72 (m, 4H), 7.65 (t, 1H), 7.58 (q, 1H), 7.52 (d, 1H), 7.73 (br s, 1H), 7.37-7.32 (m, 3H), 7.08 (d, 1H), 3.74 (d, 2H), 3.7-3.3 (m, 9H), 3.15 (m, 2H), 2.88 (s, 3H)

Example 23

4-Fluoro-*N*-(3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}phenyl) benzamide dihydrochloride salt (E23)

The **title compound** was prepared in 82% yield according to the general procedure for the preparation of the amides (Method C) starting from 3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}aniline (**D6**) and 4-fluorobenzoic acid.

HPLC/MS (ES/+): t_R= 6.45 min; assay 98.2% a/a; m/z: 469 [MH^+].$C_{29}H_{29}FN_4O$ requires 468.

^{1}H-NMR (400 MHz, d_6-DMSO) δ(ppm): 11.29 (br s, 1H), 10.36 (s, 1H), 8.96 (br s, 1 H), 8.08 (m, 2H), 7.99 (br s, 1H), 7.86 (br s, 1H), 7.62 (d, 1H), 7.47 (br d, 1H), 7.40 (m, 3H), 7.09 (d, 1H), 3.70-3.30 (m, 10H), 3.18 (dd, 2H), 2.93 (br s, 3H).

Example 24

2,4-Difluoro-*N*-(3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}phenyl) benzamide dihydrochloride salt (E24)

The **title compound** was prepared in 78% yield according to the general procedure for the preparation of the amides (Method C) starting from 3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}aniline (**D6**) and 2,4-difluorobenzoic acid.

HPLC/MS (ES/+): t_R= 6.51 min; assay >99% a/a; m/z: 487 [MH^+]. $C_{29}H_{28}F_2N_4O$ requires 486.

^{1}H-NMR (400 MHz, d_6-DMSO) δ(ppm): 11.16 (br s, 1H), 10.49 (s, 1H), 8.93 (br s, 1H), 7.70 (br s, 2H), 7.81 (br s, 2H), 7.75 (m, 1H), 7.53 (d, 1H), 7.47 (m, 2H), 7.39 (t, 1H), 7.25 (td, 1H), 7.10 (d, 1H), 3.70-3.30 (m, 10H), 2.92 (s, 3H).

Example 25

3-Fluoro-*N*-(3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}phenyl) benzamide dihydrochloride salt (E25)

The **title compound** was prepared in 91% yield according to the general procedure for the preparation of the amides (Method C) starting from 3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}aniline (**D6**) and 3-fluorobenzoic acid.
HPLC/MS (ES/+): t_R= 6.45 min; assay >99% a/a; m/z: 469 [MH^+]. $C_{29}H_{29}FN_4O$ requires 468.
^{1}H-NMR (400 MHz, d_6-DMSO) δ(ppm): 11.18 (br s, 1H), 10.41 (s, 1H), 8.94 (br s, 1H), 7.97 (br s, 2H), 7.87 (br s, 2H), 7.80 (m, 2H), 7.62 (m, 2H), 7.48 (m, 2H), 7.10 (d, 1H), 3.80-3.30 (m, 10H), 3.18 (m, 2H), 2.92 (br s, 3H).

Example 26

2,5-Difluoro-*N*-(3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}phenyl) benzamide dihydrochloride salt (E26)

The **title compound** was prepared in 82% yield according to the general procedure for the preparation of the amides (Method C) starting from 3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}aniline (**D6**) and 2,5-difluorobenzoic acid.
HPLC/MS (ES/+): t_R= 6.45 min; assay >99% a/a; m/z: 487 [MH^+]. $C_{29}H_{28}F_2N_4O$ requires 486.
^{1}H-NMR (400 MHz, d_6-DMSO) δ(ppm): 11.20 (br s, 1H), 10.54 (s, 1H), 8.91 (br s, 1 H), 7.96 (br m, 2H), 7.80 (br m, 2H), 7.56-7.40 (m, 5H), 7.36 (t, 1H), 7.09 (d, 1H), 3.80-3.10 (m, 12H), 2.90 (s, 3H).

Example 27

3,5-Difluoro-*N*-(3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}phenyl) benzamide dihydrochloride salt (E27)

The **title compound** was prepared in 74% yield according to the general procedure for the preparation of the amides (Method C) starting from 3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}aniline (**D6**) and 3,5-difluorobenzoic acid.
HPLC/MS (ES/+): t_R= 6.66 min; assay 98.6% a/a; m/z: 487 [MH^+]. $C_{29}H_{28}F_2N_4O$ requires 486.
^{1}H-NMR (400 MHz, d_6-DMSO) δ(ppm): 11.00 (br s, 1H), 10.46 (s, 1H), 8.90 (br s, 1H), 7.93 (s, 2H), 7.90 (br s, 1H), 7.72 (m, 2H), 7.86 (s, 1H), 7.62 (d, 1H), 7.56 (m, 1H), 7.45 (br s, 1H), 7.40 (t, 1H), 7.12 (d, 1H), 3.76 (d, 2H), 3.70-3.30 (m, 8H), 3.17 (m, 2H), 2.99 (br s, 3H).

Example 28

2,3-Difluoro-*N*-(3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}phenyl) benzamide dihydrochloride salt (E28)

The **title compound** was prepared in 86% yield according to the general procedure for the preparation of the amides (Method C) starting from 3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}aniline (**D6**) and 2,3-difluorobenzoic acid.
HPLC/MS (ES/+): t_R= 6.41 min, assay >99% a/a; m/z: 486 [MH^+]. $C_{29}H_{28}F_2N_4O$ requires 486.
^{1}H-NMR (400 MHz, d_6-DMSO) δ(ppm): 11.00 (br s, 1 H), 10.62 (s, 1 H), 8.95 (br s, 1 H), 7.94 (s, 2H), 7.82 (s, 1H), 7.80 (br s, 1H), 7.65 (m, 1H), 7.53 (d, 1H), 7.50 (m, 1H), 7.45 (br s, 1H), 7.39 (t, 1H), 7.38 (m, 1H), 7.12 (d, 1H), 3.76 (d, 2H), 3.70-3.30 (m, 8H), 3.17 (m, 2H), 2.96 (br s, 3H).

Example 29

2,6-Difluoro-*N*-(3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}phenyl) benzamide dihydrochloride salt (E29)

The **title compound** was prepared in 68% yield according to the general procedure for the preparation of the amides (Method C) starting from 3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}aniline (**D6**) and 2,6-difluorobenzoic acid.

HPLC/MS (ES/+): t_R= 6.24 min; assay >99% a/a; m/z: 486 [MH^+]. $C_{29}H_{28}F_2N_4O$ requires 486.

^{1}H-NMR (400 MHz, d_6-DMSO) δ(ppm): 10.90 (br s, 1H), 10.87 (s, 1H), 8.87 (br s, 1H), 7.92 (s, 2H), 7.84 (s, 1H), 7.79 (br s, 1H), 7.62 (m, 1H), 7.48 (d, 1H), 7.50 (m, 1H), 7.44 (br s, 1H), 7.39 (t, 1H), 7.27 (m, 2H), 7.12 (d, 1H), 3.76 (d, 2H), 3.70-3.30 (m, 8H), 3.17 (m, 2H), 2.88 (br s, 3H).

Example 30

3,4-Difluoro-*N*-(3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}phenyl) benzamide dihydrochloride salt (E30)

The **title compound** was prepared in 92% yield according to the general procedure for the preparation of the amides (Method C) starting from 3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}aniline (**D6**) and 3,4-difluorobenzoic acid.

HPLC/MS (ES/+): t_R= 6.66 min; assay >99% a/a; m/z: 486 [MH^+]. $C_{29}H_{28}F_2N_4O$ requires 486.

^{1}H-NMR (400 MHz, d_6-DMSO) δ(ppm): 11.04 (br s, 1H), 10.42 (s, 1H), 8.90 (br s, 1 H), 8.08 (m, 1H), 7.93 (s, 2H), 7.90 (m, 1H), 7.85 (s, 1H), 7.81 (br s, 1H), 7.65 (m, 1H), 7.62 (d, 1H), 7.45 (br s, 1H), 7.39 (t, 1H), 7.11 (d, 1H), 3.76 (d, 2H), 3.70-3.30 (m, 8H), 3.17 (m, 2H), 2.89 (br s, 3H).

Example 31

3-(Methyloxy)-*N*-(3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}phenyl) benzamide dihydrochloride salt (E31)

The **title compound** was prepared in 83% yield according to the general procedure for the preparation of the amides (Method C) starting from 3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}aniline (**D6**) and 3-(methyloxy)benzoic acid.

HPLC/MS (ES/+): t_R= 6.39 min; assay >99% a/a; m/z: 481[MH^+]. $C_{30}H_{30}N_4O_2$ requires 480.

^{1}H-NMR (400 MHz, d_6-DMSO) δ(ppm): 11.88 (br s, 1H), 10.30 (s, 1H), 8.86 (br s, 1H), 7.91 (br s, 2H), 7.87 (br s, 1H), 7.78 (br s, 2H), 7.63 (dd, 1H), 7.56 (d, 1H), 7.51 (m, 1H), 7.47 (t, 1H), 7.47 (br s, 1H), 7.38 (t, 1H), 7.19 (dm, 1H), 7.09 (d, 1H), 3.86 (s, 3H), 3.76 (d, 2H), 3.70-3.25 (m, 8H), 3.17 (m, 2H), 2.88 (br s, 3H).

Example 32

2-(Methyloxy)-*N*-(3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}phenyl) benzamide dihydrochloride salt (E32)

The **title compound** was prepared in 85% yield according to the general procedure for the preparation of the amides (Method C) starting from 3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}aniline (**D6**) and 2-(methyloxy)benzoic acid.

HPLC/MS (ES/+): t_R= 6.54 min; assay >99% a/a; m/z: 481[MH^+]. $C_{30}H_{30}N_4O_2$ requires 480.
^{1}H-NMR (400 MHz, d_6-DMSO) δ(ppm): 11.13 (br s, 1H), 10.17 (s, 1H), 8.93 (br s, 1H), 7.97 (s, 2H), 7.86-7.78 (br s, 1H), 7.64 (dd, 1H), 7.58-7.50(m, 2H), 7.47 (br s, 1H), 7.36 (t, 1H), 7.21 (d, 1H), 7.09 (dt, 1H), 7.07 (d, 1H), 3.92 (s, 3H), 3.76 (d, 2H), 3.70-3.30 (m, 8H), 3.17 (m, 2H), 2.91(br s, 3H).

Example 33

4-(Methyloxy)-*N*-(3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}phenyl) benzamide dihydrochloride salt (E33)

The **title compound** was prepared in 83% yield according to the general procedure for the preparation of the amides (Method C) starting from 3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}aniline (**D6**) and 4-(methyloxy)benzoic acid.
HPLC/MS (ES/+): t_R= 6.21 min; assay >99% a/a; m/z: 481[MH^+]. $C_{30}H_{30}N_4O_2$ requires 480.
^{1}H-NMR (500 MHz, d_6-DMSO) δ(ppm): 11.09 (br s, 1H), 10.16 (s, 1H), 8.91 (br s, 1H), 7.97 (d, 2H), 7.94 (br s, 2H), 7.84 (s, 1H), 7.81 (br s, 1H), 7.60 (d, 1H), 7.44 (br s, 1H), 7.34 (t, 1H), 7.05 (m, 3H), 3.83 (s, 3H), 3.74 (br d, 2H), 3.60-3.40 (m, 6H), 3.33 (br t, 2H), 3.14 (dd, 2H), 2.89 (br s, 3H).

Example 34

4-Cyano-*N*-(3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}phenyl) benzamide dihydrochloride salt (E34)

The **title compound** was prepared in 85% yield according to the general procedure for the preparation of the amides (Method C) starting from 3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}aniline (**D6**) and 4-cyanobenzoic acid.
HPLC/MS (ES/+): t_R= 6.15 min assay >99% a/a; m/z: 481[MH^+]. $C_{30}H_{30}N_4O_2$ requires 480.
^{1}H-NMR (500 MHz, d_6-DMSO) δ(ppm): 10.72 (br s, 1H), 10.56 (s, 1H), 8.81 (br s, 1H), 8.11 (d, 2H), 8.04 (d, 2H), 7.86 (br s, 3H), 7.75 (br s, 1H), 7.59 (d, 1H), 7.39 (br s, 1H), 7.38 (t, 1H), 7.09 (d, 1H), 3.74 (br d, 2H), 3.70-3.40 (m, 6H), 3.28 (br t, 2H), 3.14 (dd, 2H), 2.84 (br s, 3H).

Example 35

3,5-Dimethyl-*N*-(3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}phenyl)-4-isoxazolecarboxamide (E35)

The **title compound** was prepared in 56% yield according to the general procedure for the preparation of the amides (Method C) starting from 3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}aniline (**D6**) and 3,5-dimethyl-4-isoxazolecarboxylic acid.
MS: (ES/+) m/z: 470 [MH^+]. $C_{28}H_{31}N_5O_2$ requires 469.
^{1}H-NMR (400 MHz, $CDCl_3$) δ(ppm): 8.38 (d, 1H), 7.72 (d, 1H), 7.58 (t, 1H), 7.52 (br s, 1H), 7.31 (m, 2 H), 7.25 (d, 1H), 7.20 (br s, 1H), 7.08 (m, 2H), 3.14 (m, 4H), 2.90 (m, 2H), 2.81 (m, 4H), 2.76 (m, 2H), 2.73 (s, 3H), 2.68 (s, 3H), 2.52 (s, 3H).

Example 36

2-Methyl-*N*-(3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}phenyl)-4-(trifluoromethyl)-1,3-thiazole-5-carboxamide dihydrochloride salt (E36)

The **title compound** was prepared in 33% yield according to the general procedure for the preparation of the amides (Method C) starting from 3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}aniline (**D6**) and 2-methyl-4-(trifluoromethyl)-1,3-thiazole-5-carboxylic acid.
MS: (ES/+) m/z: 540 [MH^+]. $C_{28}H_{28}F_3N_5OS$ requires 539.
^{1}H-NMR (400 MHz, d_6-DMSO) δ(ppm): 10.93 (br s, 1H), 8.82 (br s, 1H), 7.88 (br s, 2H), 7.75 (br s, 1H), 7.70 (br s, 1H), 7.43 (d, 1H), 7.40 (br s, 1H), 7.36 (t, 1H), 7.10 (d, 1H), 3.8-3.2 (m, 10H), 3.12 (m, 2H), 2.85 (s, 3H), 2.75 (s, 3H).

Example 37

2-Methyl-*N*-(3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}phenyl)-1,3-thiazole-4-carboxamide dihydrochloride salt (E37)

The **title compound** was prepared in 52% yield according to the general procedure for the preparation of the amides (Method C) starting from 3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}aniline (**D6**) and 2-methyl-1,3-thiazole-4-carboxylic acid.
MS: (ES/+) m/z: 472 [MH^+]. $C_{27}H_{29}N_5OS$ requires 471.
^{1}H-NMR (400 MHz, d_6-DMSO) δ(ppm): 10.70 (br s, 1H), 10.15 (s, 1H), 8.77 (br s, 1H), 8.26 (s, 1H), 7.87 (br s, 1H), 7.75-7.85 (m, 2H), 7.39 (br s, 1H), 7.34 (t, 1H), 7.06 (d, 1H), 3.80-3.20 (m, 10H), 3.12 (dd, 2H), 2.83 (br s, 3H), 2.76 (s, 3H).

Example 38

4-Methyl-*N*-(3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}phenyl)-1,3-thiazole-5-carboxamide dihydrochloride salt

The **title compound** was prepared in 46% yield according to the general procedure for the preparation of the amides (Method C) starting from 3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}aniline (**D6**) and 4-methyl-1,3-thiazole-5-carboxylic acid.
MS: (ES/+) m/z: 472 [MH^+]. $C_{27}H_{29}N_5OS$ requires 471.
^{1}H-NMR (400 MHz, d_6-DMSO) δ(ppm): 10.83 (br s, 1H), 10.28 (s, 1H), 9.13 (s, 1H), 8.86 (br s, 1H), 7.90 (br s, 2H), 7.80-7.74 (br s-s, 2H), 7.50 (d, 1H), 7.43 (br s, 1H), 7.35 (t, 1H), 7.08 (d, 1H), 3.9-3.2 (m, 10H), 3.13 (dd, 2H), 2.87 (br s, 3H), 2.61 (s, 3H).

Example 39

1-Methyl-*N*-(3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}phenyl)-1*H*-pyrazole-5-carboxamide dihydrochloride salt (E39)

The **title compound** was prepared in 60% yield according to the general procedure for the preparation of the amides (Method C) starting from 3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}aniline (**D6**) and 1-methyl-1*H*-pyrazole-5-carboxylic acid.
MS: (ES/+) m/z: 455 [MH^+]. $C_{27}H_{30}N_6O$ requires 454.
^{1}H-NMR (400 MHz, d_6-DMSO) δ(ppm): 10.96 (br s, 1H), 10.27 (s, 1H), 8.85 (br s, 1H), 8.0-7.7 (m, 4H), 7.6-7.5 (m, 2H), 7.42 (br s, 1H), 7.6 (t, 1H), 7.10-7.08 (m, 2H), 4.09 (s, 3H), 3.74 (d, 2H), 3.51-3.29 (m, 8H), 3.14 (m, 2H), 2.87 (s, 3H).

Example 40

***N*-(3-{1-Hydroxy-2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}phenyl)-2,4-dimethyl-1,3-thiazole-5-carboxamide dihydrochloride salt (E40)**

The **title compound** was prepared in 68% yield according to the general procedure for the preparation of amides (Method C) starting from 1-(3-aminophenyl)-2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethanol (**D8**) and 2,4-dimethyl-1,3-thiazole-5-carboxylic acid.
MS: (ES/+) m/z: 502 [MH^+]. $C_{28}H_{31}N_5O_2S$ required 501.
^{1}H-NMR (400 MHz, d_6-DMSO) δ(ppm): 10.18 (2 H, br s), 8.85 (1H, br s), 7.89 (3H, s), 7.77 (1H, br s), 7.53 (1H, d), 7.37 (2H, m), 7.18 (1H, d), 6.36 (1H, br s), 5.17 (1H, dd), 3.80-3.20 (10H, m), 2.85 (3H, s), 2.64 (3H, s), 2.53 (3H, s).

Example 41

***N*-(3-{1-Hydroxy-2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}phenyl)-2-methyl-1,3-thiazole-4-carboxamide dihydrochloride salt (E41)**

The **title compound** was prepared in 82% yield according to the general procedure for the preparation of amides (Method C) starting from 1-(3-aminophenyl)-2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethanol (**D8**) and 2-methyl-1,3-thiazole-4-carboxylic acid.
MS: (ES/+) m/z : 488 [MH^+]. $C_{27}H_{29}N_5O_2S$ required 487.
^{1}H-NMR (400 MHz, d_6-DMSO) δ(ppm): 10.38 (1H, br s), 10.23 (1H, s), 8.88 (1H, br s), 8.30 (1H, s), 8.08 (1H, br s), 7.95 (2H, br s), 7.82 (1H, br s), 7.75 (1H, dd), 7.44 (1H, br s), 7.41 (1H, t), 7.22 (1H, d), 6.40 (1H, br s), 5.22 (1H, br d), 3.81 (2H, br d), 3.70-3.30 (8H, br m), 2.90 (3H, br s), 2.79 ppm (3H, s).

Example 42

***N*-(3-{1-Hydroxy-2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}phenyl)-1,5-dimethyl-1*H*-pyrazole-3-carboxamide dihydrochloride salt (E42)**

The **title compound** was prepared in 95% yield according to the general procedure for the preparation of amides (Method C) starting from 1-(3-aminophenyl)-2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethanol (**D8**) and 1,5-dimethyl-1*H*-pyrazole-3-carboxylic acid.
MS: (ES/+) m/z: 485 [MH^+]. $C_{28}H_{32}N_6O_2$ required 484.
^{1}H-NMR (400 MHz, d_6-DMSO) δ(ppm): 10.30 (1H, br s), 9.97 (1H, s), 8.86 (1H, br s), 8.08 (1H, s), 7.92 (2H, br s), 7.79 (1H, br s), 7.69 (1H, d), 7.43 (1H, br s), 7.38 (1H, t), 7.17 (1H, d), 6.58 (1H, s), 6.38 (1H, br s), 5.19 (1H, br d), 3.86 (3H, s), 3.80 (2H, br m), 3.70-3.20 (8H, br m), 2.89 (3H, br s), 2.33 ppm (3H, s).

Example 43

***N*-(3-{2-[4-(2-Methyl-5-quinolinyl)-1-piperazinyl]ethyl}phenyl)methanesulfonamide (E43)**

Methanesulfonyl chloride (8 μL; 1.2 eq) was added dropwise to a solution of 3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}aniline (**D6**)(0.03 g; 1 eq) in pyridine (0.5 mL). The reaction was stirred at r.t. overnight. The reaction mixture was concentrated under reduced

pressure, diluted with water (1 mL) and a saturated aqueous solution of sodium hydrogen carbonate (1 mL), extracted into dichloromethane (3x2 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude was purified by flash chromatography, eluting with a gradient from dichloromethane to dichloromethane/MeOH (98/2) affording the **title compound** in 44% yield (0.016 g).
MS; (ES) m/z: 425.4 $[MH]^+$. $C_{23}H_{28}N_4O_2S$ requires 424.
^{1}H-NMR (300 MHz, MeOD) δ(ppm): 8.40 (d, 1 H), 7.55 (m, 2 H), 7.30 (d, 1 H), 7.15 (t, 1 H), 7.10 (m, 2 H), 6.90 ((bt, 2 H), 3.05 (bt, 4 H), 2.85 (s, 3 H), 2.83-2.63 (bm, 8 H), 2.60 (s, 3 H).

Example 44
***N*-(3-{2-[4-(2-Methyl-5-quinolinyl)-1-piperazinyl]ethyl}phenyl)-1-propanesulfonamide (E44)**
The **title compound** was prepared in 62% yield using a similar procedure to example **E43** starting from 3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}aniline (**D6**) and propanesulfonyl chloride.
MS; (ES) m/z: 453.4 $[MH]^+$. $C_{25}H_{32}N_4O_2S$ requires 452.
^{1}H-NMR (300 MHz, $CDCl_3$) δ(ppm): 8.35 (d, 1 H), 7.70 (d, 1 H), 7.60 (t, 1 H), 7.30 (m, 2 H), 7.1 (m, 2H), 7.01 (d, 1 H), 3.30 (bm, 6 H), 2.80 (bm, 6 H), 2.60 (s, 3 H), 1.80 (m, 2 H), 1.0 (t, 3 H)..

General procedure for the preparation of carbamates and their corresponding dihydrochloride salts starting from 3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}aniline (D6): Method D
Diisopropylethylamine (1.5 eq) and a chloroformate (1.2eq) were added sequentially to a stirred solution of 3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}aniline (**D6**)(1 eq) in dichloromethane at 0 °C. The solution was stirred for 1 hr at room temperature, then diluted with dichloromethane and washed with a saturated aqueous solution of NH_4Cl and brine and then dried over Na_2SO_4. The solution was concentrated under reduced pressure. The crude material was purified on SPE cartridge (Silica) eluting with a gradient from dichloromethane/MeOH 99/1 to dichloromethane/MeOH 98/2 affording the final compound (yields ranged from 43 to 78%).
The free base could be converted into its dihydrochloride salt by dissolving the compound in dichloromethane and adding a 1M ethereal solution of HCl (2.1 eq) dropwise. A yellow solid precipitated and the suspension was stirred for 15 min. The solvent was removed under reduced pressure affording a crude material which was triturated with Et_2O. The final compound was then recovered by filtration (yield quantitative).

Example 45
Methyl (3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}phenyl)carbamate (E45)

The **title compound** was prepared in 41% yield according to the general procedure for the preparation of carbamates (Method D) starting from 3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}aniline (**D6**) and methyl chloroformate.
MS; (ES) m/z: 405.4 $[MH]^+$. $C_{24}H_{28}N_4O_2$ requires 404.
^{1}H-NMR (300 MHz, $CDCl_3$) δ(ppm): 8.33 (d, 1 H), 7.70 (d, 1 H), 7.6 (t, 1 H), 7.30 (bs, 1 H), 7.25 (t, 1 H), 7.22 (dd, 1 H), 7.20 (d, 1 H), 7.10 (d, 1 H), 6.95 (dd, 1 H), 6.55 (bs, 1 H), 3.8 (s, 3 H), 3.28 (bm, 4 H), 3.28 (t, 2 H), 2.85 (t, 2 H), 2.75 (bm, 4 H), 2.66 (s, 3 H).

Example 46
Ethyl (3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}phenyl)carbamate dihydrochloride (E46)
The **title compound** was prepared in 79% yield according to the general procedure for the preparation of carbamates (Method D) starting from 3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}aniline (**D6**) and ethyl chloroformate.
MS: (ES) m/z: 419 $[MH^+]$. $C_{25}H_{30}N_4O_2$ requires 418.
^{1}H-NMR (400 MHz, d_6-DMSO) δ(ppm): 11.00 (bs, 1H), 9.74 (s, 1H), 8.95 (s, 1H), 8.00 (s, 2H), 7.87 (s, 1H), 7.57 (s, 1H), 7.51 (bs, 1H), 7.36 (m, 2H), 7.02 (d, 1H), 4.21 (q, 2H), 3.80 (d, 2H), 3.7-3.3 (m 8H), 3.17 (m, 2H), 2.96 (bs, 3H), 1.33 (t, 3H).

Example 47
Propyl (3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}phenyl)carbamate dihydrochloride (E47)
The **title compound** was prepared in 78% yield according to the general procedure for the preparation of carbamates (Method D) starting from 3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}aniline (**D6**) and propyl chloroformate.
MS: (ES) m/z: 433 $[MH^+]$. $C_{26}H_{32}N_4O_2$ requires 432.
^{1}H-NMR (400 MHz, d_6-DMSO) δ(ppm): 10.88 (bs, 1H), 9.65 (s, 1H), 8.84 (bs, 1H), 7.89 (bs, 2H), 7.76 (bs, 1H), 7.47 (s, 1H), 7.40 (bs, 1H), 7.27-6.92 (m-d, 3H), 4.02 (t, 2H), 3.8-3.2 (bm, 10 H), 3.07 (dd, 2H), 2.85 (bs, 3H), 1.62 (m, 2H), 0.91 (t, 3H).

Example 48
1-Methylethyl (3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}phenyl)carbamate dihydrochloride (E48)
The **title compound** was prepared in 77% yield according to the general procedure for the preparation of carbamates (Method D) starting from 3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}aniline (**D6**) and 1-methylethyl chloridocarbonate.
MS: (ES) m/z: 433 $[MH^+]$. $C_{26}H_{32}N_4O_2$ requires 432.
^{1}H-NMR (400 MHz, d_6-DMSO) δ(ppm): 10.98 (bs, 1H), 9.58 (s, 1H), 8.86 (bs, 1H), 7.91 (bs, 2H), 7.77 (bs, 1H), 7.48 (s, 1H), 7.42 (bs, 1H), 7.25 (m, 2H), 6.91 (d, 1H), 4.87 (m, 1H), 3.75-3.2 (bm, 10H), 3.07 (dd, 2H), 2.87 (bs, 3H), 1.24 (d, 6H).

Example 49

2-Methylpropyl (3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}phenyl) carbamate dihydrochloride (E49)

The **title compound** was prepared in 70% yield according to the general procedure for the preparation of carbamates (Method D) starting from 3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}aniline (**D6**) and 2-methylpropyl chloridocarbonate.

MS: (ES) m/z: 447 [MH^+]. $C_{27}H_{34}N_4O_2$ requires 446.

^{1}H-NMR (400 MHz, d_6-DMSO) δ(ppm): 10.94 (bs, 1H), 9.64 (s, 1H), 8.86 (s, 1H), 7.91 (s, 2H), 7.77 (s, 1H), 7.48 (s, 1H), 7.41 (bs, 1H), 7.28 (m, 2H), 6.93 (d, 1H), 3.85 (q, 2H), 3.70 (d, 2H), 3.7-3.25 (m, 8H), 3.07 (m, 2H), 2.86 (bs, 3H), 1.09 (m, 1H), 0.92 (d, 6H).

Example 50

Phenyl (3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}phenyl)carbamate dihydrochloride (E50)

The **title compound** was prepared in 59% yield according to the general procedure for the preparation of carbamates (Method D) starting from 3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}aniline (**D6**) and phenyl chloridocarbonate.

MS: (ES) m/z: 467 [MH^+]. $C_{29}H_{30}N_4O_2$ requires 466.

^{1}H-NMR (400 MHz, d_6-DMSO) δ(ppm): 10.95 (bs, 1H), 10.27 (s, 1H), 8.84 (s, 1H), 7.90 (s, 2H), 7.75 (s, 1H), 7.52 (s, 1H), 7.4-7.2 (m, 8H), 7.00 (d, 1H), 3.71 (d, 2H), 3.7-3.3 (m, 8H), 3.09 (m, 2H), 2.86 (bs, 3H)

Example 51

Phenylmethyl (3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}phenyl)carbamate dihydrochloride (E51)

The **title compound** was prepared in 43% yield according to the general procedure for the preparation of carbamates (Method D) starting from 3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}aniline (**D6**) and phenylmethyl chloridocarbonate.

MS: (ES) m/z: 481 [MH^+]. $C_{30}H_{32}N_4O_2$ requires 480.

^{1}H-NMR (400 MHz, d_6-DMSO) δ(ppm): 10.8 (bs, 1H), 9.8 (s, 1H), 8.9 (bs, 1H), 7.9 (bs, 2H), 7.76 (bs, 1H), 7.50 (bs, 1H), 7.4-7.2 (m, 8H), 6.95 (d, 1H), 5.15 (s, 2H), 3.72 (bd, 2H), 3.6-3.2 (m, 8H), 3.09 (m, 2H), 2.86 (bs, 3H).

General procedure for the preparation of ureas or thioureas and their corresponding dihydrochloride salts starting from 3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}aniline (D6): Method E

An isocyanate or isothiocyanate (1 eq) was added to a stirred solution of3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}aniline (**D6**) (1 eq) in dichloromethane at room temperature under an inert atmosphere, and the reaction was left under stirring for 16 h. The solution was then poured into water and extracted with dichloromethane, the organic phase was dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude material was purified on SPE cartridge (Silica) using a gradient from dichloromethane to

dichloromethane/MeOH 95/5 as eluant affording the final compound (yields ranged from 30 to 80%).
The free base could be converted into its dihydrochloride salt by dissolving the compound in Et_2O and MeOH and adding an 1M ethereal solution of HCl (2.1 eq) dropwise. A yellow solid precipitated and the suspension was stirred for 15 min. The solvent was removed under reduced pressure affording a crude material which was triturated with Et_2O. The final compound was then recovered by filtration (yield quantitative).

General procedure for the preparation of ureas and their corresponding dihydrochloride salts starting from 3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl] ethyl}aniline(D6): Method F
Triethylamine(6 eq) and solid triphosgene (0.5eq) were in added sequentially to a stirred solution of 3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}aniline (**D6**)(1eq) in dichloromethane at 0°C under an inert atmosphere. The reaction mixture was left under stirring for 1h then diisopropylethylamine and an amine (1.1 eq) dissolved in CH_3CN were added dropwise. The solution was stirred for 16 h then diluted with dichloromethane, washed with saturated aqueous solutions of $NaHCO_3$ and brine and dried over Na_2SO_4. The solution was concentrated under reduced pressure and the crude material was purified on SPE cartridge (Silica) eluting with a gradient from dichloromethane to dichloromethane/MeOH 98/2 affording the final compound (yields ranged from 20 to 50%).
The free base could be converted into its dihydrochloride salt by dissolving the compound in Et_2O and MeOH and adding an 1M ethereal solution of HCl (2.1 eq) dropwise. A yellow solid precipitated and the suspension was stirred for 15 min. The solvent was removed under reduced pressure affording a crude material which was triturated with Et_2O. The final compound was then recovered by filtration (yield quantitative).

Example 52
***N*-(3,5-Difluorophenyl)-*N'*-(3-{2-[4-(2-methylquinolin-5-yl)piperazin-1-yl]ethyl}phenyl)urea dihydrochloride (E52)**
The **title compound** was prepared in 40% yield according to the general procedure for the preparation of ureas (Method E) starting from 3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}aniline (**D6**) and 1,3-difluoro-5-isocyanatobenzene.
MS:(ES/+) m/z: 502 [MH^+] $C_{29}H_{29}F_2N_5O$ requires 501.
^{1}H-NMR (400MHz, d_6-DMSO) δ(ppm): 10.8 (bs, 1 H), 9.71 (s, 1 H), 9.29 (s, 1H), 8.9(bs, 1 H), 7.94 (bs, 2 H), 7.82 (bs, 1H), 7.53 (s, 1 H), 7.45 (bs, 1 H), 7.31 (d, 2 H), 7.20 (dd, 2H), 6.97 (t, 1 H), 6.80 (tt, 1 H), 3.70 (bd, 2 H), 3.7-3.2 (m, 8 H), 3.13 (dd, 2 H), 2.90 (bs, 3H).

Example 53
***N*-(2-Chlorophenyl)-*N'*-(3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}phenyl)urea dihydrochloride (E53)**

The **title compound** was prepared in 55% yield according to the general procedure for the preparation of ureas (Method E) starting from 3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}aniline (**D6**) and 1-chloro-2-isocyanatobenzene.
MS: (ES/+) m/z: 500 [MH^+] $C_{29}H_{30}ClN_5O$ requires 499.
^{1}H-NMR (400MHz, d_6-DMSO) δ(ppm): 10.89 (bs, 1 H), 9.66(s, 1 H), 8.86 (bs, 1 H), 8.41 (s, 1 H), 8.14 (dd, 1 H), 7.90 (bs, 2 H), 7.78 (bs, 1 H), 7.54 (d, 1 H), 7.40 (bs, 1 H), 7.43 (dd, 1 H), 7.27 (m, 3H), 7.02(dt, 1 H), 6.93 (m, 1 H), 3.71(d, 2 H), 3.6-3.2 (m, 8 H), 3.10 (m, 2 H), 2.86 (bs, 3 H).

Example 54
***N*-(3-Chlorophenyl)-*N'*-(3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}phenyl)urea dihydrochloride (E54)**
The **title compound** was prepared in 52% yield according to the general procedure for the preparation of ureas (Method E) starting from 3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}aniline (**D6**) and 1-chloro-3-isocyanatobenzene.
MS: (ES/+) m/z: 500 [MH^+] $C_{29}H_{30}ClN_5O$ requires 499.
^{1}H-NMR (400MHz, d_6-DMSO) δ(ppm): 10.53 (bs, 1 H), 9.34 (s, 1 H), 9.15 (s, 1H), 8.81(bs, 1 H), 7.88 (bs, 2 H), 7.76 (t, 1H), 7.74 (bs, 1 H), 7.57 (s, 1 H), 7.41 (bs, 1 H), 7.30 (m, 4H), 7.03 (dt, 1 H), 6.96 (bd, 1 H), 3.76 (bd, 2 H), 3.6-3.2 (m, 8 H), 3.11 (dd, 2 H), 2.85 (bs, 3H).

Example 55
***N*-(3-Fluorophenyl)-*N'*-(3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}phenyl)urea dihydrochloride (E55)**
The **title compound** was prepared in 48% yield according to the general procedure for the preparation of ureas (Method E) starting from 3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}aniline (**D6**) and 1-fluoro-3-isocyanatobenzene.
MS: (ES/+) m/z: 484[MH^+] $C_{29}H_{30}FN_5O$ requires 483.
^{1}H-NMR (400MHz, d_6-DMSO) δ(ppm): 10.7(bs, 1 H), 9.47 (s, 1 H), 9.24 (s, 1H), 8.75 (bs, 1 H), 7.81 (bs, 2 H), 7.68 (bs, 1H), 7.50 (d+bs, 2 H), 7.44 (bs, 1 H), 7.31 (t, 1 H), 7.3-7.24 (m, 2 H), 7.09 (d, 1 H), 6.89 (d, 1 H), 6.74 (td, 1 H), 3.7-3.2(m, 10 H), 3.07 (m, 2 H), 2.8 (bs, 3 H).

Example 56
***N*-(4-Fluorophenyl)-*N'*-(3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}phenyl)urea dihydrochloride (E56)**
The **title compound** was prepared in 64% yield according to the general procedure for the preparation of ureas (Method E) starting from 3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}aniline (**D6**) and 1-fluoro-4-isocyanatobenzene.
MS: (ES/+) m/z: 484[MH^+]. $C_{29}H_{30}FN_5O$ requires 483.
^{1}H-NMR (400MHz, d_6-DMSO) δ(ppm): 10.49(bs, 1 H), 9.40 (s, 1 H), 8.96 (s, 1H), 8.77(bs, 1 H), 7.83 (bs, 2 H), 7.71 (bs, 1H), 7.51(bs, 1 H), 7.45 (dd, 2 H), 7.37 (bs, 1 H), 7.25 (bd, 2 H), 7.10 (t, 2 H), 6.90 (bt, 1 H), 3.8-3.2(m, 10 H), 3.06 (dd, 2 H), 2.81 (bs, 3 H).

Example 57

***N*-(2-Fluorophenyl)-*N'*-(3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}phenyl)urea dihydrochloride (E57)**

The **title compound** was prepared in 75% yield according to the general procedure for the preparation of ureas (Method E) starting from 3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}aniline (**D6**) and 1-fluoro-2-isocyanatobenzene.

MS: (ES/+) m/z: 484[MH^+] $C_{29}H_{30}FN_5O$ requires 483.

^{1}H-NMR (400MHz, d_6-DMSO) δ(ppm): 10. 9(bs, 1 H), 9.36 (s, 1 H), 8.8 (bs, 1H), 8.67 (s, 1 H), 8.11 (t, 1 H), 7.86 (bs, 2H), 7.71 (bs, 1 H), 7.49 (d, 1 H), 7.37 (bs, 1 H), 7.26 (m, 2 H), 7.20 (dd, 1 H), 7.07 (dd, 1 H), 6.98 (m, 1 H), 6.90 (m, 1 H), 3.69 (d, 2 H), 3.5-3.2(m, 8 H), 3.09 (m, 2 H), 2.82 (bs, 3 H).

Example 58

***N*-[4-(Methyloxy)phenyl]-*N'*-(3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}phenyl)urea dihydrochloride (E58)**

The **title compound** was prepared in 54% yield according to the general procedure for the preparation of ureas (Method E) starting from 3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}aniline (**D6**) and 1-isocyanato-4-(methyloxy)benzene.

MS: (ES/+) m/z: 496[MH^+] $C_{30}H_{33}N_5O2$ requires 495.

^{1}H-NMR (400MHz, d_6-DMSO) δ(ppm): 10.66(bs, 1 H), 8.92 (s, 1 H), 8.82 (bs, 1H), 8.80(s, 1 H), 7.88 (bs, 2 H), 7.76 (bs, 1H), 7.50(bs, 1 H), 7.39 (bs, 1 H), 7.24 (m, 2 H), 6.88 (m, 1 H), 7.34 (d, 2 H), 6.84(d, 2 H), 3.72(m, 2 H), 3.69 (s, 3 H), 3.6-3.0 (m, 10 H), 2.81 (bs, 3 H).

Example 59

***N*-[3-(Methyloxy)phenyl]-*N'*-(3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}phenyl)urea dihydrochloride (E59)**

The **title compound** was prepared in 58% yield according to the general procedure for the preparation of ureas (Method E) starting from 3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}aniline (**D6**) and 1-isocyanato-3-(methyloxy)benzene.

MS: (ES/+) m/z: 496[MH^+] $C_{30}H_{33}N_5O2$ requires 495.

^{1}H-NMR (400MHz, d_6-DMSO) δ(ppm): 10.54(bs, 1 H), 9.00 (s, 1 H), 8.99 (s, 1H), 8.80(bs, 1 H), 7.91 (t, 1 H), 7.85 (bs, 2 H), 7.73 (bs, 1H), 7.52(bs, 1 H), 7.39 (bs, 1H), 7.25 (m, 2 H), 7.15 (t, 1 H), 6.90(m, 1 H), 3.72(m, 2 H), 3.69 (s, 3 H), 3.6-3.0 (m, 10 H), 2.81 (bs, 3 H).

Example 60

***N*-[2-(Methyloxy)phenyl]-*N'*-(3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}phenyl)urea dihydrochloride (E60)**

The **title compound** was prepared in 42% yield according to the general procedure for the preparation of ureas (Method E) starting from 3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}aniline (**D6**) and 1-isocyanato-2-(methyloxy)benzene.

MS (ES/+) m/z: 496[MH^+] $C_{30}H_{33}N_5O_2$ requires 495.

^{1}H-NMR (400MHz, d_6-DMSO) δ(ppm): 10.77 (bs, 1 H), 9.43 (s, 1 H), 8.83 (bs, 1 H), 8.26 (s, 1 H), 8.10 (dd, 1 H), 7.88 (bs, 2 H), 7.75 (bs, 1 H), 7.56 (s, 1 H), 7.40 (bs, 1 H), 7.24 (m, 2 H), 7.0-6.8 (m, 4 H), 3.86 (s, 3 H), 3.72 (d, 2 H), 3.6-3.2 (m, 8 H), 3.08 (m, 2 H), 2.84 (bs, 3 H).

Example 61

***N*-(3-{2-[4-(2-Methyl-5-quinolinyl)-1-piperazinyl]ethyl}phenyl)-*N'*-[2-(trifluoromethyl)phenyl]urea dihydrochloride (E61)**

The **title compound** was prepared in 63% yield according to the general procedure for the preparation of ureas (Method E) starting from 3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}aniline (**D6**) and 1-isocyanato-2-(trifluoromethyl)benzene.

MS (ES/+) m/z: 534[MH^+] $C_{30}H_{30}F_3N_5O$ requires 533.

^{1}H-NMR (400MHz, d_6-DMSO) δ(ppm): 10.83 (bs, 1 H), 9.54(s, 1 H), 8.83 (bs, 1 H), 8.15 (s, 1 H), 8.14 (dd, 1 H), 7.88 (bs, 2 H), 7.73 (bs, 1 H), 7.64 (d, 1 H), 7.59 (t, 1 H), 7.50 (s, 1 H), 7.38 (bs, 1 H), 7.25 (m, 3 H), 6.91 (m, 1 H), 3.69 (m, 2 H), 3.6-3.2 (m, 8 H), 3.07 (m, 2 H), 2.83 (bs, 3 H).

Example 62

***N*-(3-{2-[4-(6-Methyl-1-naphthalenyl)-1-piperazinyl]ethyl}phenyl)-*N'*-[3-(trifluoromethyl)phenyl]urea dihydrochloride (E62)**

The **title compound** was prepared in 23% yield according to the general procedure for the preparation of ureas (Method E) starting from 3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}aniline (**D6**) and 1-isocyanato-3-(trifluoromethyl)benzene.

MS: (ES/+) m/z: 534[MH^+] $C_{31}H_{31}F_3N_4O$ requires 533.

^{1}H-NMR (400MHz, d_6-DMSO) δ(ppm): 10.41 (bs, 1 H), 9.47 (s, 1 H), 9.16 (s, 1H), 8.81 (bs, 1 H), 8.08 (s, 1 H), 7.86 (bs, 2 H), 7.72 (bs, 1 H), 7.61 (s, 1 H), 7.6-7.5 (m, 2 H), 7.41 (bs, 1 H), 7.35-7.25 (m, 3 H), 6.97 (d, 1 H), 3.76 (bm, 2 H), 3.7-3.3 (bm, 6H), 3.27 (bm, 2 H), 3.11 (m, 2 H), 2.85 (bs, 3 H).

Example 63

***N*-(3-{2-[4-(2-Methyl-5-quinolinyl)-1-piperazinyl]ethyl}phenyl)-*N'*-[4-(trifluoromethyl)phenyl]urea dihydrochloride (E63)**

The **title compound** was prepared in 45% yield according to the general procedure for the preparation of ureas (Method E) starting from 3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}aniline (**D6**) and 1-isocyanato-4-(trifluoromethyl)benzene.

MS: (ES/+) m/z: 534[MH^+] $C_{30}H_{30}F_3N_5O$ requires 533.

^{1}H-NMR (400MHz, d_6-DMSO) δ(ppm): 10.34 (bs, 1 H), 9.45 (s, 1 H), 9.12 (s, 1H), 8.71 (bs, 1 H), 7.81 (t, 1 H), 7.63 (m, 5 H), 7.54 (s, 1 H), 7.53 (bs, 1 H), 7.27 (bs, 2 H), 6.93 (bd, 1 H), 3.8-3.1 (bm, 10 H), 3.07 (dd, 2 H), 2.79 (bs, 3 H).

Example 64

***N*-(3-{2-[4-(2-Methyl-5-quinolinyl)-1-piperazinyl]ethyl}phenyl)-*N'*-propylurea dihydrochloride (E64)**

The **title compound** was prepared in 53% yield according to the general procedure for the preparation of ureas (Method E) starting from 3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}aniline (**D6**) and 1-isocyanatopropane.
MS: (ES/+) m/z: 432[MH^+] $C_{26}H_{33}N_5O$ requires 431.
^{1}H-NMR (400MHz, d_6-DMSO) δ(ppm): 10.5 (bs, 1 H), 8.75 (bs, 1 H), 8.54 (s, 1H), 7.83 (bs, 2 H), 7.7 (bs, 1 H), 7.45 (s, 1 H), 7.38 (bs, 1 H), 7.18 (m, 2 H), 6.81 (d, 1 H), 6.23 (bt, 1 H), 3.7-3.25 (bd, bt, 4 H), 3.6-3.3 (m, 4 H), 3.4-3.02 (m, m, 6 H), 2.81 (bs, 3 H), 1.41 (m, 2 H), 0.85 (t, 3 H).

Example 65
***N*-(1,1-Dimethylethyl)-*N'*-(3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}phenyl)urea dihydrochloride (E65)**
The **title compound** was prepared in 79% yield according to the general procedure for the preparation of ureas (Method E) starting from 3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}aniline (**D6**) and 2-isocyanato-2-methylpropane.
MS: (ES/+) m/z: 446[MH^+] $C_{27}H_{35}N_5O$ requires 445.
^{1}H-NMR (400MHz, d_6-DMSO) δ(ppm): 10.48 (bs, 1 H), 8.75 (bs, 1 H), 8.37 (s, 1H), 7.83 (bs, 2 H), 7.7 (bs, 1 H), 7.51 (s, 1 H), 7.38 (bs, 1 H), 7.17 (t, 1 H), 7.04 (dd, 1 H), 6.79 (d, 1 H), 6.08 (s, 1 H), 3.71-3.24 (bd, bt, 4 H), 3.6-3.3 (m, 4 H), 3.40 (m, 2 H), 3.02 (m, 2 H), 2.81 (bs, 3 H), 1.27 (s, 9 H).

Example 66
***N*-(3-{2-[4-(2-Methyl-5-quinolinyl)-1-piperazinyl]ethyl}phenyl)-*N'*-(phenylmethyl)urea dihydrochloride (E66)**
The **title compound** was prepared in 68% yield according to the general procedure for the preparation of ureas (Method E) starting from 3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}aniline (**D6**) and (isocyanatomethyl)benzene.
MS: (ES/+) m/z: 480 [MH^+] $C_{30}H_{33}N_5O$ requires 479.
^{1}H-NMR (400MHz, d_6-DMSO) δ(ppm): 10.74 (bs, 1 H), 8.84(bs, 1 H), 8.76 (s, 1 H), 7.88 (bs, 2 H), 7.75 (bs, 1 H), 7.48 (s, 1 H), 7.40 (bs, 1 H), 7.32 (m, 4 H), 7.20 (m, 3 H), 6.80 (m, 1 H), 6.77 (t, 1 H), 4.28(d, 2 H), 3.70 (d, 2 H), 3.71(d, 2 H), 3.6-3.2 (m, 8 H), 3.04 (m, 2 H), 2.85 (bs, 3 H).

Example 67
***N*-Methyl-*N'*-(3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}phenyl)-*N*-phenylurea dihydrochloride (E67)**
The **title compound** was prepared in 47% yield according to the general procedure for the preparation of ureas (Method F) starting from 3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}aniline (**D6**) and *N*-methylaniline.
MS: (ES/+) m/z: 480 [MH^+]. $C_{30}H_{33}N_5O$ requires 479.

^{1}H-NMR (400MHz, d_6-DMSO) δ(ppm): 10.9 (bs, 1 H), 8.85(bs, 1 H), 8.14 (s, 1 H), 7.9 (bs, 2 H), 7.75 (bs, 1 H), 7.44-7.36(m, 4 H), 7.32-7.25 (m, 3 H), 7.24 (d, 1 H), 7.20 (t, 1 H), 6.88(d, 1 H), 3.69 (bd, 2 H), 3.6-3.2(m, 8 H), 3.26 (s, 3 H), 3.05(m, 2 H), 2.85 (bs, 3 H).

Example 68

***N*-(3-{2-[4-(2-Methyl-5-quinolinyl)-1-piperazinyl]ethyl}phenyl)-*N'*-phenylurea dihydrochloride (E68)**

The **title compound** was prepared in 73% yield according to the general procedure for the preparation of ureas (Method E) starting from 3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}aniline (**D6**) and isocyanatobenzene.

MS: (ES/+) m/z: 466 [MH^+] $C_{29}H_{31}N_5O$ requires 465.

^{1}H-NMR (500MHz, d_6-DMSO) δ(ppm): 10.4 (bs, 1 H), 8.95(bd, 2 H), 8.75 (bs, 1 H), 7.83 (bs, 2 H), 7.7 (bs, 1 H), 7.54 (s, 1 H), 7.45 (dd, 2 H), 7.38 (bs, 1 H), 7.27 (m, 4 H), 6.96(m, 1 H), 6.91 (m, 1 H), 3.73 (bd, 2 H), 3.6-3.3(m, 6 H), 3.24 (t, 2 H), 3.08 (dd, 2 H), 2.81 (bs, 3 H).

Example 69

***N*-cyclohexyl-*N'*-(3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}phenyl)urea dihydrochloride (E69)**

The **title compound** was prepared in 64% yield according to the general procedure for the preparation of ureas (Method E) starting from 3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}aniline (**D6**) and isocyanatocyclohexane.

MS: (ES/+) m/z: 472 [MH^+] $C_{29}H_{37}N_5O$ requires 471.

^{1}H-NMR (400MHz, d_6-DMSO) δ(ppm): 8.84 (bs, 1 H), 8.5 (bd, 1 H), 7.9 (bs, 2 H), 7.78 (bs, 1 H), 7.4 (bs, 2 H), 7.26 (m, 2 H), 6.8 (d, 1 H), 6.2 (bd, 1 H), 3.7-3.2 (m, 11 H), 3.03 (dd, 2 H), 2.85 (bs, 3 H), 1.8 (m, 2 H), 1.65 (m, 2 H), 1.5 (m, 1 H), 1.25 (m, 3 H), 1.15 (m, 2 H).

Example 70

***N*-Ethyl-*N'*-(3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}phenyl)thiourea dihydrochloride (E70)**

The **title compound** was prepared in 74% yield according to the general procedure for the preparation of ureas (Method E) starting from 3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}aniline (**D6**) and isothiocyanatoethane.

MS:(ES/+) m/z: 434 [MH^+] $C_{25}H_{31}N_5S$ requires 433.

^{1}H-NMR (400MHz, d_6-DMSO) δ(ppm): 11.11 (bs, 1 H), 9.73 (bs, 1 H), 8.93 (bs, 1 H), 7.99 (m, 3 H), 7.82 (bd, 1 H), 7.44 (s, 2 H), 7.30 (m, 2 H), 7.03 (dd, 1 H), 3.8-3.2 (m, 12 H), 3.1(m, 2 H), 2.9 (bs, 3 H), 1.10 (t, 3 H).

Example 71

***N*-(3-{2-[4-(2-Methyl-5-quinolinyl)-1-piperazinyl]ethyl}phenyl)-*N'*-[2-(2-thienyl)ethyl]urea dihydrochloride (E71)**

The **title compound** was prepared in 46% yield according to the general procedure for the preparation of ureas (Method E) starting from 3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}aniline (**D6**) and 2-(2-isocyanatoethyl)thiophene.
MS: (ES/+) m/z: 500 [MH^+] $C_{28}H_{33}N_5OS$ requires 499.
^{1}H-NMR (400MHz, d_6-DMSO) δ(ppm): 10.48 (bs, 1 H), 8.75 (bs, 1 H), 8.64(s, 1 H), 7.83 (m, 3 H), 7.68 (bs, 1 H), 7.48 (bs, 1 H), 7.36 (bs, 1 H), 7.33 (dd, 1 H), 7.19 (t, 1 H), 7.15 (dt, 1 H), 6.95 (dd, 1 H), 6.89 (m, 1 H), 6.82 (dt, 1 H), 6.3 (t, 1 H), 3.71 (bd, 2 H), 3.6-3.2 (m, 12 H), 3.02(m, 2 H), 2.95 (bs, 2 H), 2.81 (bs, 3 H).

Example 72
***N*-(3-{2-[4-(2-Methyl-5-quinolinyl)-1-piperazinyl]ethyl}phenyl)-*N'*-phenylthiourea dihydrochloride (E72)**
The **title compound** was prepared in 59% yield according to the general procedure for the preparation of ureas (Method E) starting from 3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}aniline (**D6**) and isothiocyanatobenzene.
MS: (ES/+) m/z: 482[MH^+] $C_{29}H_{31}N_5S$ requires 481.
^{1}H-NMR (400MHz, d_6-DMSO) δ(ppm): 10.55 (bs, 1 H), 10.09 (s, 1 H), 10.07 (s, 1 H), 8.75 (bs, 1 H), 7.83 (bs, 2 H), 7.68 (bs, 1 H), 7.51 (s, 1 H), 7.49 (d, 2 H), 7.4-7.3 (m, 2 H), 7.35 (bs, 1 H), 7.31 (t, 2 H), 7.10 (t, 1 H), 7.06 (d, 1 H), 3.71 (d, 2 H), 3.5-3.2 (m, 8 H), 3.09 (m, 2 H), 2.80 (bs, 3 H).

Example 73
***N*-Cyclopentyl-*N'*-(3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}phenyl)urea dihydrochloride (E73)**
The **title compound** was prepared in 96% yield according to the general procedure for the preparation of ureas (Method E) starting from 3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}aniline (**D6**) and isocyanatocyclopentane.
MS (ES/+) m/z: 458 [MH^+] $C_{28}H_{35}N_5O$ requires 457.
^{1}H-NMR (400MHz, d_6-DMSO) δ(ppm): 10.94 (bs, 1 H), 8.89 (bs, 1 H), 8.51 (s, 1 H), 7.93 (bs, 2 H), 7.80 (bd, 1 H), 7.43 (bs, 2 H), 7.17 (m,2 H), 6.81 (m, 1 H), 6.35 (bd, 1 H), 3.90 (m, 1 H), 3.8-3.2 (bm, 10 H), 3.04 (dd, 2 H), 2.88 (bs, 3 H), 1.80 (m, 2 H), 1.62 (m, 2 H), 1.51 (m, 2 H), 1.34 (m, 2 H).

Example 74
***N*-(1-Methylpropyl)-*N'*-(3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}phenyl)urea dihydrochloride (E74)**
The **title compound** was prepared in 60% yield according to the general procedure for the preparation of ureas (Method E) starting from 3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}aniline (**D6**) and 2-isocyanatobutane.
MS: (ES/+) m/z: 446 [MH^+] $C_{27}H_{35}N_5O$ requires 445.

^{1}H-NMR (400MHz, d_6-DMSO) δ(ppm): 11.07 (bs, 1 H), 8.91 (bs, 1 H), 8.57 (s, 1 H), 7.95 (bm, 2 H), 7.81 (bd, 1 H), 7.43 (bs, 2 H), 7.17 (m,2 H), 6.80 (m, 1 H), 6.17 (bd, 1 H), 3.8-3.2 (bm, 11 H), 3.06 (dd, 1 H), 2.89 (bs, 3 H), 1.39 (q, 1 H), 1.04 (d, 3 H), 0.85 (t, 3 H).

Example 75

***N*-Ethyl-*N'*-(3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}phenyl)urea dihydrochloride (E75)**

The **title compound** was prepared in 95% yield according to the general procedure for the preparation of ureas (Method E) starting from 3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}aniline (**D6**) and isocyanatoethane.

MS: (ES/+) m/z: 418 [MH^+] $C_{25}H_{31}N_5O$ requires 417.

^{1}H-NMR (400MHz, d_6-DMSO) δ(ppm): 10.89 (bs, 1 H), 8.60 (bs, 1 H), 8.90 (s, 1 H), 7.92 (bs, 2 H), 7.80(bs, 1 H), 7.44 (s, 2 H), 7.19 (m, 2 H), 6.81 (m, 1 H), 3.71 (d, 2 H), 3.6-3.2 (m, 10 H), 3.07 (m, 2 H), 2.87 (bs, 3 H), 1.02 (t, 3 H).

Example 76

***N*-(2-Methylphenyl)-*N'*-(3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}phenyl)urea dihydrochloride (E76)**

The **title compound** was prepared in 60% yield according to the general procedure for the preparation of ureas (Method E) starting from 3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}aniline (**D6**) and 1-isocyanato-2-methylbenzene.

MS: (ES/+) m/z: 480 [MH^+] $C_{30}H_{33}N_5O$ requires 479.

^{1}H-NMR (400MHz, d_6-DMSO) δ(ppm): 10.65 (bs, 1 H), 9.37 (s, 1 H), 8.80 (d, 1 H), 8.13 (s, 1 H), 7.85 (m, 2 H), 7.79 (d, 1 H), 7.72 (bs, 1 H), 7.52 (s, 1 H), 7.37 (bs, 1 H), 7.25 (m, 1 H), 7.09 (m, 2 H), 6.88 (m, 2 H), 3.69 (d, 2 H), 3.6-3.2 (m, 6 H), 3.06 (m, 2 H), 2.81 (bs, 3 H), 2.22 (s, 3 H).

Example 77

***N*-[3,5-Bis(trifluoromethyl)phenyl]-*N'*-(3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}phenyl)urea dihydrochloride (E77)**

The **title compound** was prepared in 60% yield according to the general procedure for the preparation of ureas (Method E) starting from 3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}aniline (**D6**) and 1-isocyanato-3,5-bis(trifluoromethyl)benzene.

MS:(ES/+) m/z: 602 [MH^+] $C_{31}H_{29}F_6N_5O$ requires 601.

^{1}H-NMR (400MHz, d_6-DMSO) δ(ppm): 10.6 (b, 1 H), 10.06 (s, 1 H), 9.41 (s, 1 H), 8.85 (bs, 1 H), 8.15 (s, 2 H), 7.9 (bs, 2 H), 7.78 (bs, 1 H), 7.66 (s, 1 H), 7.6 (s, 1 H), 7.43 (bs, 1 H), 7.32 (d, 2 H), 6.99 (t, 1 H), 3.76 (bd, 2 H), 3.4-3.7 (bm, 6 H), 3.29 (t, 2 H), 3.13 (dd, 2 H), 2.87 (bs, 3 H).

Example 78

***N*-Methyl-*N*-(3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}phenyl)-*N'*-phenylurea dihydrochloride salt.**

The **title compound** was prepared in 85% yield according to general procedure for the preparation of ureas (Method E) starting from *N*-methyl-3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}aniline (**D7**) and isocyanatobenzene.
MS: (ES) m/z: 480 [MH^+]. $C_{30}H_{35}Cl_2N_5O$ requires 479.
^{1}H-NMR (400 MHz, d_6-DMSO) δ(ppm): 10.90 (1H, bs), 8.80 (1H, bs), 8.18 (1H, s), 7.88 (2H, bs), 7.75 (1H, bs), 7.43 (2H, d), 7.37(1H, d), 7.43 (1H, d), 7.30 (1H, bs), 7.25-7.15 (2H, m), 7.19 (2H, dt), 6.92 (1H, tt), 3.69 (4H, br d), 3.60-3.20 (6H, m), 3.28 (3H, s), 3.12 (2H, m), 2.85 (2H, s).

Example 79
1-(3-{2-[4-(2-Methyl-5-quinolinyl)-1-piperazinyl]ethyl}phenyl)-3-phenyl-2-imidazolidinone dihydrochloride salt (E79)
The **title compound** was prepared in 50% yield according to the general procedure for the preparation of ureas from arylbromides (Method A) starting from 5-{4-[2-(3-bromophenyl)ethyl]-1-piperazinyl}-2-methylquinoline (**D14**) and 1-phenyl-2-imidazolidinone using 3.0 equiv. of CuI and N,N'-dimethylethylenediamine.
MS: (ES/+) m/z: 492 [MH^+]. $C_{31}H_{33}N_5O$ requires 491.
^{1}H-NMR (400 MHz, d_6-DMSO) δ(ppm):11.0 (1H, br s), 8.90 (1H, br s), 7.94 (2H, br s), 7.80 (1H, br s), 7.71 (1H, br s), 7.66 (2H, d), 7.51 (1H, br d), 7.39 (1H, m), 7.09 (1H, m), 7.05 (1H, d), 4.01 (4H, s), 3.80-3.20 (10H, m), 3.17 (2H, dd), 2.90 (2H, br s).

Example 80
1-[4-(Methyloxy)phenyl]-3-(3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl} phenyl)-2-imidazolidinone dihydrochloride salt (E80)
The **title compound** was prepared in 16% yield according to the general procedure for the preparation of ureas from arylbromides (Method A) starting from 5-{4-[2-(3-bromophenyl)ethyl]-1-piperazinyl}-2-methylquinoline (**D14**) and 1-[4-(methyloxy)phenyl]-2-imidazolidinone using 6.0 equiv. of CuI and N,N'-dimethylethylenediamine, which were added in two different portions of 3.0 equiv.
MS: (ES/+) m/z: 522 [MH^+]. $C_{23}H_{35}N_5O_2$ requires 521.
^{1}H-NMR (400 MHz, d_6-DMSO) δ(ppm): 10.57 (1H, br s), 8.76 (2H, br s), 7.84 (2H, br s), 7.69 (1H, br s), 7.68 (1H, s), 7.52 (d, 2H), 7.46 (d, 1H), 7.37 (br s, 1H), 7.36 (t, 1H), 7.01 (1H, d), 6.94 (2H, d), 3.95 (4H, s), 3.74 (3H, s), 3.72-3.13 (12H, m), 2.82 (3H, br s).

Example 81
1-[2-(Methyloxy)phenyl]-3-(3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}phenyl)-2-imidazolidinone dihydrochloride salt (E81)
The **title compound** was prepared in 65% yield according to the general procedure for the preparation of ureas from arylbromides (Method A) starting from 5-{4-[2-(3-bromophenyl)ethyl]-1-piperazinyl}-2-methylquinoline (**D14**) and 1-[2-(methyloxy)phenyl]-2-imidazolidinone using 6.0 equiv. of CuI and N,N'-dimethylethylenediamine, which were added in two different portions of 3.0 equiv.

MS: (ES/+) m/z: 522 [MH^+]. $C_{23}H_{35}N_5O_2$ requires 521.
^{1}H-NMR (400 MHz, d_6-DMSO) δ(ppm): 10.93 (1H, br s), 8.88 (1H, br s), 7.93 (2H, br s), 7.79 (1H, br s), 7.67 (1H, br s), 7.48 (1H, dd), 7.44 (1H, br s), 7.37 (1H, t), 7.32 (2H, m), 7.14 (1H, br d), 7.01 (2H, m), 4.00 (2H, dd), 3.86 (2H, m), 3.84 (3H, s), 3.75 (2H, br d), 3.70-3.20 (8H, m), 3.15 (2H, dd), 2.89 (3H, br s).

Example 82
1-(2-Methylphenyl)-3-(3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}phenyl)-2-imidazolidinone dihydrochloride salt (E82)
The **title compound** was prepared in 65% yield according to the general procedure for the preparation of ureas from arylbromides (Method A) starting from 5-{4-[2-(3-bromophenyl)ethyl]-1-piperazinyl}-2-methylquinoline (**D14**) and 1-(2-methylphenyl)-2-imidazolidinone using 3.0 equiv. of CuI and N,N'-dimethylethylenediamine.
MS: (ES/+) m/z : 506 [MH^+]. $C_{32}H_{35}N_5O$ requires 505.
^{1}H-NMR (400 MHz, d_6-DMSO) δ(ppm): 10.90 (1H, br s), 8.90 (1H, br s), 7.93 (br s, 2H), 7.80 (1H, br s), 7.67 (1H, s), 7.49 (dd, 1H), 7.44 (1H, br s), 7.40-7.20 (m, 5H), 7.02 (1H, dd), 4.03 (2H, t), 3.88 (2H, t), 3.74 (2H, br d), 3.70-3.20 (8H, m), 3.15 (2H, dd), 2.89 (3H, br s), 2.26 (3H, s).

Example 83
1-(3-Methylphenyl)-3-(3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}phenyl)-2-imidazolidinone dihydrochloride salt (E83)
The **title compound** was prepared in 55% yield according to the general procedure for the preparation of ureas from arylbromides (Method A) starting from 5-{4-[2-(3-bromophenyl)ethyl]-1-piperazinyl}-2-methylquinoline (**D14**) and 1-(3-methylphenyl)-2-imidazolidinone using 10 mol% of CuI and N,N'-dimethylethylenediamine.
MS: (ES/+) m/z : 506 [MH^+]. $C_{32}H_{35}N_5O$ requires 505.
^{1}H-NMR (400 MHz, d_6-DMSO) δ(ppm): 10.80 (1H, br s), 8.85 (1H, br s), 7.89 (2H, br s), 7.76 (1H, br s), 7.70 (1H, s), 7.48 (1H, s), 7.45 (1H, d), 7.42 (2H, br m), 7.37 (1H, t), 7.24 (1H, t), 7.02 (1H, d), 6.89 (1H, d), 3.98 (4H, s), 3.74 (2H, br d), 3.60-3.30 (8H, m), 3.14 (2H, dd), 2.86 (3H, br s), 2.32 (3H, s).

Example 84
1-(4-Methylphenyl)-3-(3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}phenyl)-2-imidazolidinone dihydrochloride salt (E84)
The **title compound** was prepared in 65% yield according to the general procedure for the preparation of ureas from arylbromides (Method A) starting from 5-{4-[2-(3-bromophenyl)ethyl]-1-piperazinyl}-2-methylquinoline (**D14**) and 1-(4-methylphenyl)-2-imidazolidinone using 3.0 equiv. of CuI and N,N'-dimethylethylenediamine.
MS: (ES/+) m/z : 506 [MH^+]. $C_{32}H_{35}N_5O$ requires 505.
^{1}H-NMR (400 MHz, d_6-DMSO) δ(ppm):10.94 (1H, br s), 8.90 (1H, br s), 7.94 (2H, br s), 7.80 (1H, br s), 7.71 (1H, br s), 7.53 (2H, d), 7.49 (22H, d), 7.45 (1H, br s), 7.38 (1H, t), 7.19 (2H,

d), 7.04 (1H, d), 3.99 (4H, s), 3.75 (2H, br d), 3.70-3.30 (8H, m), 3.16 (2H, dd), 2.90 (3H, br s), 2.00 (3H, s).

General procedure for the synthesis of cyclic ureas and carbamates and their corresponding dihydrochloride salts starting from 3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}aniline (D3): Method G

Diisopropylethylamine (1.5 eq) and a chloroformate or isocyanate (1.2eq) were added sequentially to a stirred solution of 3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}aniline (1 eq) in dichloromethane at 0 °C. The solution was stirred for 1 hr at room temperature, then diluted with dichloromethane and washed with a saturated aqueous solution of NH_4Cl and brine and then dried over Na_2SO_4. The solution was concentrated under reduced pressure. The crude material was dissolved in dimethylformamide, cooled to 0 °C, and NaH (1.1 eq) was added portionwise under an inert atmosphere. The mixture was stirred for 2 hrs at room temperature, then the solvent was removed by means of an SCX cartridge. The crude material was purified on SPE cartridge (Silica) eluting with a gradient from dichloromethane/MeOH 99/1 to dichloromethane/MeOH 98/2 affording the final compound (yields ranged from 22 to 87%).

The free base could be converted into its dihydrochloride salt by dissolving the compound in Et_2O and MeOH and adding an 1M ethereal solution of HCl (2.1 eq) dropwise. A yellow solid precipitated and the suspension was stirred for 15 min. The solvent was removed under reduced pressure affording a crude material which was triturated with Et_2O. The final compound was then recovered by filtration (yield quantitative).

Example 85

1-(3-{2-[4-(2-Methyl-5-quinolinyl)-1-piperazinyl]ethyl}phenyl)-2-imidazolidinone dihydrochloride (E85)

The **title compound** was prepared in 22% yield according to the general procedure for the synthesis of cyclic ureas and carbamates (Method G) starting from 3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}aniline (**D3**) and 1-chloro-2-isocyanatoethane.

MS: (ES) m/z: 416 [MH^+]. $C_{25}H_{29}N_5O$ requires 415.

^{1}H-NMR (400 MHz, d_6-DMSO) δ(ppm): 10.60 (bs, 1H), 8.77 (s, 1H), 7.85 (s, 2H), 7.71 (s, 1H), 7.59 (s, 1H), 7.38 (dd, 1H), 7.28 (t, 1H), 6.96 (bs, 1H), 6.92 (d, 1H), 3.83 (m, 2H), 3.71 (d, 2H), 3.7-3.2 (m, 10H), 3.08 (m, 2H), 2.82 (bs, 3H).

Example 86

3-(3-{2-[4-(2-Methyl-5-quinolinyl)-1-piperazinyl]ethyl}phenyl)-1,3-oxazolidin-2-one dihydrochloride (E86)

The **title compound** was prepared in 81% yield according to the general procedure for the synthesis of cyclic ureas and carbamates (Method G) starting from 3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}aniline (**D3**) and (2-bromoethyl)carbamic chloride.

MS: (ES) m/z: 417 [MH^+]. $C_{25}H_{28}N_4O_2$ requires 416.

^{1}H-NMR (400 MHz, d_6-DMSO) δ(ppm): 10.99 (bs, 1H), 8.87 (bm, 1H), 7.91 (bm, 2H), 7.79 (bm, 1H), 7.57 (s, 1H), 7.40 (m, 3H), 7.08 (d, 1H), 4.43 (t, 2H), 4.07 (t, 2H), 3.72-3.3 (m, 10H), 3.15 (m, 2H), 2.87 (bs, 3H).

Example 87

1-(3-{2-[4-(2-Methyl-5-quinolinyl)-1-piperazinyl]ethyl}phenyl)tetrahydro-2(1*H*)-pyrimidinone dihydrochloride (E87)

The **title compound** was prepared in 87% yield according to the general procedure for the synthesis of cyclic ureas and carbamates (Method G) starting from 3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}aniline (**D3**) and 1-chloro-3-isocyanatopropane.
MS: (ES) m/z: 430 [MH$^+$]. $C_{26}H_{31}N_5O$ requires 429.
^{1}H-NMR (400 MHz, d_6-DMSO) δ(ppm): 11.05 (bs, 1H), 8.94 (s, 1H), 7.97 (s, 2H), 7.84 (d, 1H), 7.46 (bs, 1H), 7.30 (m, 2H), 7.19 (dd, 1H), 7.08 (d, 1H), 6.58 (s, 1H), 3.70 (bm, 4H), 3.63 (t, 2H), 3.6-3.3 (bm, 6H), 3.24 (t, 2H), 3.12 (m, 2H), 2.91 (s, 3H), 1.95 (t, 2H).

Example 88

3-(3-{2-[4-(2-Methyl-5-quinolinyl)-1-piperazinyl]ethyl}phenyl)tetrahydro-2*H*-1,3-oxazin-2-one dihydrochloride (E88)

The **title compound** was prepared in 75% yield according to the general procedure for the synthesis of cyclic ureas and carbamates (Method G) starting from 3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}aniline (**D3**) and (3-chloropropyl)carbamic chloride. MS: (ES) m/z: 431 [MH$^+$]. $C_{26}H_{30}N_4O_2$ requires 430.
^{1}H-NMR (400 MHz, d_6-DMSO) δ(ppm): 10.89 (bs, 1H), 8.84 (bm, 1H), 7.89 (bm, 2H), 7.76 (bm, 1H), 7.40 (m, 4H), 7.31 (s, 1H), 4.32 (t, 2H), 3.72-3.3 (m, 10H), 3.66 (t, 2H), 3.13 (m, 2H), 2.85 (bs, 3H), 2.10 (m, 2H).

General procedure for the synthesis of cyclic amide, urea, and carbamate derivatives of 1-(3-aminophenyl)-2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethanol (D8) and their corresponding dihydrochloride salts starting form 1-(3-acetylphenyl)-2-cyclic amides, ureas and carbamates. Method H

$AlCl_3$ (1% w/w) and then bromine (1 eq) was added dropwise to a stirred solution of a 1-(3-acetylphenyl)-2-cyclic amide, urea or carbamate (1 eq) in Et_2O or dichloromethane at 0 °C. The solution was stirred for 1 hr at room temperature, then diluted with dichloromethane and washed with a saturated aqueous solution of $NaHCO_3$, a saturated aqueous solution of NH_4Cl and brine and then dried over Na_2SO_4. The solution was concentrated under reduced pressure. The crude material was dissolved in dimethylformamide and 2-methyl-5-(1-piperazinyl)quinoline (**D3**) (1 eq) and Na_2CO_3 (1.5 eq) were added. The solution was stirred for 2-4 hrs at room temperature. MeOH was then added in equal volume with respect to dimethylformamide, followed by $NaBH_4$ (2 eq) and the solution was stirred for 15 min at room temperature. The solvent was removed by means of an SCX cartridge. The crude material was purified on SPE cartridge (Silica) eluting with a gradient from dichloromethane/MeOH

99/1 to dichloromethane/MeOH 98/2 affording the final compound (yields ranged from 39 to 71%).
The free base could be converted into its dihydrochloride salt by dissolving the compound in Et_2O and MeOH and adding an 1M ethereal solution of HCl (2.1 eq) dropwise. A yellow solid precipitated and the suspension was stirred for 15 min. The solvent was removed under reduced pressure affording a crude material which was triturated with Et_2O. The final compound was then recovered by filtration (yield quantitative).

Example 89
1-(3-{1-Hydroxy-2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}phenyl)-2-pyrrolidinone dihydrochloride (E89)
The **title compound** was prepared in 25% yield according to the general procedure for the synthesis of cyclic amide, urea and carbamate derivatives of 1-(3-aminophenyl)-2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethanol (Method H) starting from 1-(3-acetylphenyl)-2-pyrrolidinone (**D9**) and 2-methyl-5-(1-piperazinyl)quinoline (**D3**).
MS: (ES) m/z: 431 [MH^+]. $C_{26}H_{30}N_4O_2$ requires 430.
^{1}H-NMR (400 MHz, d_6-DMSO) δ(ppm): 10.2 (bs, 1H), 8.8 (bs, 1H), 7.86 (bs, 2H), 7.81 (s, 1H), 7.73 (bs, 1H), 7.54 (dd, 1H), 7.40 (t, 1H), 7.38 (bs, 1H), 7.20 (d, 1H), 6.36 (bs, 1H), 5.18 (dd, 1H), 3.83 (t, 2H), 3.76 (bt, 2H), 3.7-3.2 (m, 8H), 2.83 (bs, 3H), 2.5 (m, 2H), 2.07 (q, 2H).

Example 90
1-(3-{1-Hydroxy-2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}phenyl)-2-azetidinone dihydrochloride (E90)
The **title compound** was prepared in 39% yield according to the general procedure for the synthesis of cyclic amide, urea and carbamate derivatives of 1-(3-aminophenyl)-2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethanol (Method H) starting from 1-(3-acetylphenyl)-2-azetidinone (**D10**) and 2-methyl-5-(1-piperazinyl)quinoline (**D3**).
MS: (ES) m/z: 417 [MH^+]. $C_{25}H_{28}N_4O_2$ requires 416.
^{1}H-NMR (400 MHz, d_6-DMSO) δ(ppm): 10.35 (bs, 1H), 8.84 (bs, 1H), 7.91 (bs, 2H), 7.77 (bs, 1H), 7.51 (s, 1H), 7.40 (t+bs, 2H), 7.23 (d, 1H), 7.15 (d, 1H), 6.38 (bs, 1H), 5.19 (d, 1H), 3.8-3.2 (m, 12H), 3.09 (t, 2H), 2.86 (bs, 3H).

Example 91
3-(3-{1-Hydroxy-2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}phenyl)-1,3-oxazolidin-2-one dihydrochloride (E91)
The **title compound** was prepared in 34% yield according to the general procedure for the synthesis of cyclic amide, urea and carbamate derivatives of 1-(3-aminophenyl)-2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethanol (Method H) starting from 1-(3-acetylphenyl)-1,3-oxazolidin-2-one (**D11**) and 2-methyl-5-(1-piperazinyl)quinoline (**D3**).
MS: (ES) m/z: 433 [MH^+]. $C_{25}H_{28}N_4O_3$ requires 432.

^{1}H-NMR (400 MHz, d_6-DMSO) δ(ppm): 10.3 (bs, 1H), 8.8 (bs, 1H), 7.89 (bs, 2H), 7.76 (bs, 2H), 7.44 (m, 3H), 7.20 (d, 1H), 6.4 (bs, 1H), 5.21 (dd, 1H), 4.45 (t, 2H), 4.06 (t, 2H), 3.76 (bt, 2H), 3.7-3.2 (m, 8H), 2.85 (bs, 3H).

Example 92

1-(3-{1-Hydroxy-2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}phenyl)-2-imidazolidinone dihydrochloride (E92)

The **title compound** was prepared in 26% yield according to the general procedure for the synthesis of cyclic amide, urea and carbamate derivatives of 1-(3-aminophenyl)-2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethanol (Method H) starting from 1-(3-acetylphenyl)-2-imidazolidinone (**D12**) and 2-methyl-5-(1-piperazinyl)quinoline (**D3**).

MS: (ES) m/z: 432 [MH^+]. $C_{25}H_{29}N_5O_2$ requires 431.

^{1}H-NMR (400 MHz, d_6-DMSO) δ(ppm): 10.2 (bs, 1H), 8.8 (bs, 1H), 7.87 (bs, 2H), 7.74 (bs, 2H), 7.43 (dd, 1H), 7.40 (bs, 1H), 7.33 (t, 1H), 7.06 (d, 1H), 6.98 (bs, 1H), 6.3 (bs, 1H), 5.14 (dd, 1H), 3.84 (t, 2H), 3.78 (bt, 2H), 3.7-3.0 (m, 10H), 2.84 (bs, 3H).

Example 93

1-(3-{2-[4-(2-Methyl-5-quinolinyl)-1-piperazinyl]ethyl}phenyl)-2,5-pyrrolidinedione (E93)

Dihydro-2,5-furandione (2 eq) was added to a stirred solution of 3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}aniline (**D6**)(1 eq) in toluene/pyridine (3:2) at room temperature under an inert atmosphere. The solution was stirred for 30 min at room temperature, then irradiated in a microwave reactor (PersonalChemistry Emrys™ Optimiser, 300W, 170°C, 20 min, 4 cycles), diluted with dichloromethane and washed with a saturated aqueous solution of NH_4Cl and brine and then dried over Na_2SO_4. The solution was concentrated under reduced pressure. The crude material was purified on SPE cartridge (Silica) eluting with a gradient from dichloromethane/MeOH 99/1 to dichloromethane/MeOH 98/2 affording the final compound in 76% yield.

The free base was converted into its dihydrochloride salt by dissolving the compound in Et_2O and MeOH and adding an 1M ethereal solution of HCl (2.1 eq) dropwise. A yellow solid precipitated and the suspension was stirred for 15 min. The solvent was removed under reduced pressure affording a crude material which was triturated with Et_2O to give the **title compound.**

MS: (ES) m/z: 429 [MH^+]. $C_{26}H_{28}N_4O_2$ requires 428.

^{1}H-NMR (400 MHz, d_6-DMSO) δ(ppm): 11.1 (bs, 1H), 8.91 (bs, 1H), 7.94 (bs, 2H), 7.81 (bs, 1H), 7.49 (t, 1H), 7.44 (bs, 1H), 7.37 (d, 1H), 7.22 (s, 1H), 7.18 (d, 1H), 3.73 (bm, 2H), 3.59 (bm, 2H), 3.48 (bm, 4H), 3.33 (m, 2H), 3.19 (m, 2H), 2.89 (bs, 3H), 2.80 (bs, 4H).

Example 94

***N*-(3-{2-[4-(7-Chloro-2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}phenyl)acetamide dihydrochloride (E94)**

The **title compound** was prepared in 65% yield according to the general procedure for the preparation of the amides (Method B) starting from 3-{2-[4-(7-Chloro-2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}aniline (**D18**) and acetyl chloride.
MS: (ES) m/z: 423 [MH^+]. $C_{24}H_{27}ClN_4O$ requires 422.
^{1}H-NMR (400 MHz, d_6-DMSO) δ(ppm): 10.68 (bs, 1H), 9.99 (s, 1H), 8.53 (bs, 1H), 7.80 (s, 1H), 7.65 (s, 1H), 7.58 (d, 1H), 7.37 (d, 1H), 7.28 (m, 2H), 6.97 (d, 1H), 4-3.2 (bm, 10H), 3.07 (dd, 1H), 2.74 (s, 3H), 2.04 (s, 3H).

Example 95
***N*-(3-{2-[4-(7-chloro-2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}phenyl)methanesulfonamide dihydrochloride (E95)**
The **title compound** was prepared in 65% yield using a similar procedure to example **E43** starting from 3-{2-[4-(7-Chloro-2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}aniline (**D18**) and methanesulfonyl chloride.
MS: (ES) m/z: 459 [MH^+]. $C_{23}H_{27}ClN_4O_2S$ .2HCl requires 458.
^{1}H-NMR (400 MHz, d_6-DMSO) δ(ppm): 10.69 (bs, 1H), 9.80 (s, 1H), 8.53 (d, 1H), 7.79 (s, 1H), 7.58 (d, 1H), 7.33 (t, 1H), 7.27 (s, 1H), 7.15 (d, 1H), .7.11 (d, 1H), 7.05 (d, 1H), 3.7-3.2 (bm, 10H), 3.09 (dd, 2H), 3.01 (s, 3H), 2.73 (s, 3H).

Example 96
***N*^{1},*N*^{1}-Dimethyl-*N*^{2}-(3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}phenyl)glycinamide pyrrolidinedione dihydrochloride (E96)**
Diisopropylethylamine (2 eq), NaI (2 eq) and 2-chloro-*N*,*N*-dimethylacetamide (1.1eq) were added sequentially to a stirred solution of 3-{2-[4-(7-chloro-2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}aniline (1 eq) in dimethylformamide at room temperature under an inert atmosphere. The solution was stirred for 2 hrs at 60°C, then the solvent was removed by means of an SCX cartridge. The crude material was purified on SPE cartridge (Silica) eluting with a gradient of dichloromethane/MeOH 99/1 to dichloromethane/MeOH 98/2 affording the final compound in 38% yield.
The free base was converted into its dihydrochloride salt by dissolving the compound in Et_2O and MeOH and adding an 1M ethereal solution of HCl (2.1 eq) dropwise. A yellow solid precipitated and the suspension was stirred for 15 min. The solvent was removed under reduced pressure affording a crude material which was triturated with Et_2O to give the **title compound.**
MS: (ES) m/z: 466 [MH^+]. $C_{26}H_{32}ClN_5O$ requires 465.
^{1}H-NMR (500 MHz, CD_3OD) δ(ppm): 9.19 (d, 1H), 7.95 (d, 1H), 7.90 (d, 1H), 7.62 (d, 1H), 7.45 (t, 1H), 7.32 (bs, 1H), 7.25 (bd, 1H), 7.19 (bd, 1H), 4.37 (bs, 2H), 3.85 (bd, 2H), 3.65 (bm, 4H), 3.60 (dd, 2H), 3.45 (bt, 2H), 3.25 (dd, 2H), 3.06 (s, 3H), 3.02 (s, 3H), 3.01 (s, 3H).

Example 97
2-Methyl-5-(4-{[3-(1*H*-pyrazol-1-yl)phenyl]acetyl}-1-piperazinyl)quinoline (E97)

EDC•HCl (1.5 eq), HOBt (2 eq) and 2-methyl-5-(1-piperazinyl)quinoline (**D3**)(1 eq) were added sequentially to a stirred solution of [3-(1*H*-pyrazol-1-yl)phenyl]acetic acid (**D19**)(1.1 eq) in dimethylformamide at room temperature under an inert atmosphere. The solvent was removed by means of an SCX cartridge. The crude material was purified on SPE cartridge (Silica) eluting with a gradient from dichloromethane/MeOH 99/1 to dichloromethane/MeOH 98/2 affording the **title compound** in 74% yield.
MS: (ES) m/z: 412 [MH^+]. $C_{25}H_{25}N_5O$ requires 411.
^{1}H-NMR (400 MHz, $CDCl_3$) δ(ppm): 8.36 (d, 1H), 7.93 (d, 1H), 7.75 (d, 1H), 7.71 (s, 1H), 7.69 (s, 1H), 7.58 (d, 1H), 7.55 (t, 1H), 7.42 (t, 1H), 7.25 (m, 2H), 7.00 (d, 1H), 6.46 (s, 1H), 3.87 (s, 2H), 4.0-3.7 (m, 4H), 3.1-2.9 (m, 4H), 2.72 (s, 3H).

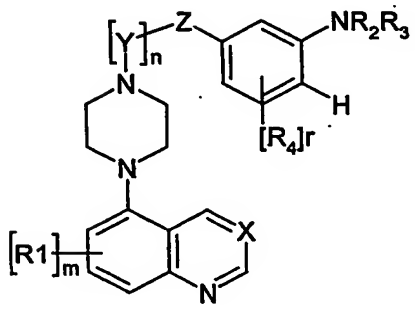
Example 98

2-Methyl-5-(4-{2-[3-(1*H*-pyrazol-1-yl)phenyl]ethyl}-1-piperazinyl)quinoline (E98)

A 1M tetrahydrofuran solution of borane-tetrahydrofuran complex (3 eq) was added to a stirred solution of 2-methyl-5-(4-{[3-(1*H*-pyrazol-1-yl)phenyl]acetyl}-1-piperazinyl)quinoline (**E97**)(1 eq) in tetrahydrofuran at room temperature under an inert atmosphere. The solution was heated to 60 °C for 3 hrs. An aqueous 3N solution of HCl was added and the solution was stirred at room temperature for 12 hrs. The solvent was removed under reduced pressure. The crude material was purified by SCX cartridge affording the **title compound** in 52% yield.
MS: (ES) m/z: 398 [MH^+]. $C_{25}H_{27}N_5$ requires 397.
^{1}H-NMR (300 MHz, $CDCl_3$) δ(ppm): 8.35 (d, 1H), 7.90 (d, 1H), 7.70 (d, 1H), 7.70 (s, 1H), 7.65 (t, 1H), 7.60 (t, 1H), 7.50 (dd, 1H), 7.35 (t, 1H), 7.25 (d, 1H), 7.15 (d, 1H), 7.05 (d, 1H), 6.45 (t, 1H), 3.20 (m, 4H), 3.0-2.7 (m, 8), 2.70 (s, 3H).

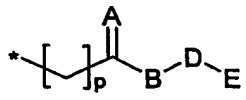
Claims

1. A compound of formula (I) or a pharmaceutically acceptable salt thereof:



(I)

wherein:
R1 is halogen, cyano, C_{1-6}alkyl, C_{1-6}alkoxy, haloC1-6alkoxy or haloC_{1-6}alkyl;
m is 0, 1, 2, 3 or 4;
r is 0, 1, 2, 3 or 4;
X is N or CH;
n is 1, 2, 3 or 4;
Y is $-CH_2-$, -CH(C_{1-6}alkyl)- or -C(C_{1-6}alkyl)(C_{1-6}alkyl);
Z is $-CH_2-$, -CHOH-, -CHR5- or -CR5R6-;
R2 and R3 are independently hydrogen, C_{1-6}alkyl, C_{1-6}alkylsulfonyl or a group having the formula (II):



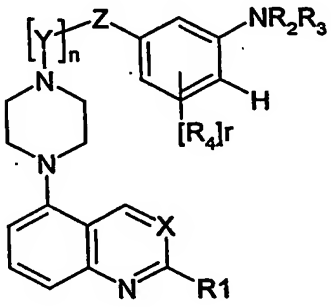
(II)

wherein p is 0, 1, 2, 3 or 4;
A is oxygen or sulfur;
B is a single bond or -NR7- wherein R7 is hydrogen, C_{1-6}alkyl or an optionally substituted aryl;
D is $-(CH_2)_q-$, $-(CH_2)_qO-$ or $-O(CH_2)_q-$, wherein q is 0, 1, 2, 3 or 4; and
E is C_{1-6}alkyl, haloC_{1-6}alkyl, an optionally substituted C_{3-7}cycloalkyl, an optionally substituted aryl, or E is -NR8R9 (wherein R8 and R9 are independently selected from hydrogen, C_{1-6}alkyl and optionally substituted aryl)

or R2 and R3, together with the nitrogen atom to which R2 and R3 are attached, combine to form an optionally substituted 3-7 membered monocyclic hetercyclic group;

and R4, R5 and R6 are independently halogen, cyano, C_{1-6}alkyl or C_{1-6}alkoxy.

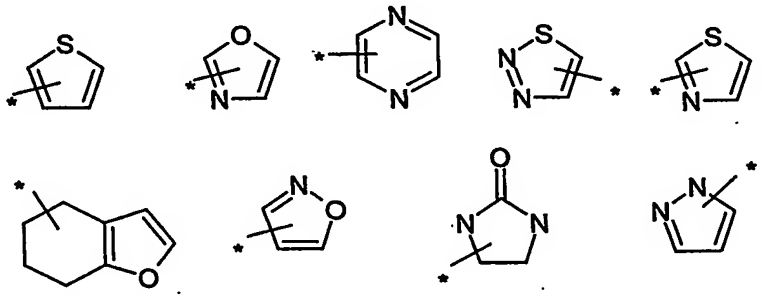
2. A compound as claimed in claim 1, wherein m is 1 and R1 is attached at the following position:



3. A compound as claimed in claim 1 or claim 2, wherein when E is methylamine, ethylamine, propylamine, isopropylamine, butylamine, isobutylamine, sec-butylamine, tert-butylamine, pentylamine, neopentylamine, sec-pentylamine, n-pentylamine, isopentylamine, tert-pentylamine, hexylamine; dimethylamine, diethylamine, dipropylamine, diisopropylamine, dibutylamine, diisobutylamine, disec-butylamine, ditert-butylamine, dipentylamine, dineopentylamine, dihexylamine, butylmethylamino, isopropylmethylamino, ethylisopropylamino, ethylmethylamino; a monoarylamino such as anilino; or a monoC_{1-6}alkyl-monoarylamino such as -N(CH_3)phenyl.

4. A compound as claimed in claim 1 or claim 2, wherein E is a 5- to 7- membered monocyclic aromatic ring, or a 9- to 10- membered bicyclic aromatic ring, wherein one or more of the carbon atoms in the ring(s) is optionally replaced by a heteroatom independently selected from nitrogen, oxygen and sulfur, wherein the ring is optionally substituted by one or more substituents independently selected from oxo, halogen, C_{1-6}alkyl, CF_3, cyano, hydroxy, C_{1-6}alkanoyl, and C_{1-6}alkoxy.

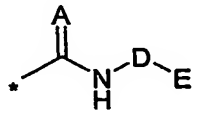
5. A compound as claimed in claim 4, wherein E is seleted from:



wherein any of these groups may be substituted by 1, 2 or 3 substituents selected from CF_3, C_{1-6}alkoxy, C_{1-6}alkyl, oxo and halogen.

6. A compound as claimed in claim 1 or 2, wherein E is phenyl, optionally substituted by 1, 2 or 3 substituents selected from CF_3, C_{1-6}alkoxy, C_{1-6}alkyl and halogen.

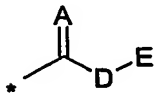
7. A compound as claimed in any of claims 1-6, wherein R2 and R3 are independently:



(IIa)

wherein A is oxygen or sulfur, D is $-(CH_2)_r-$, $-(CH_2)_rO-$ or $-O(CH_2)_r-$ wherein r is 0, 1, 2, 3, or 4, and E is C_{1-6}alkyl, an optionally substituted C_{3-7}cycloalkyl or an optionally substituted aryl;

or

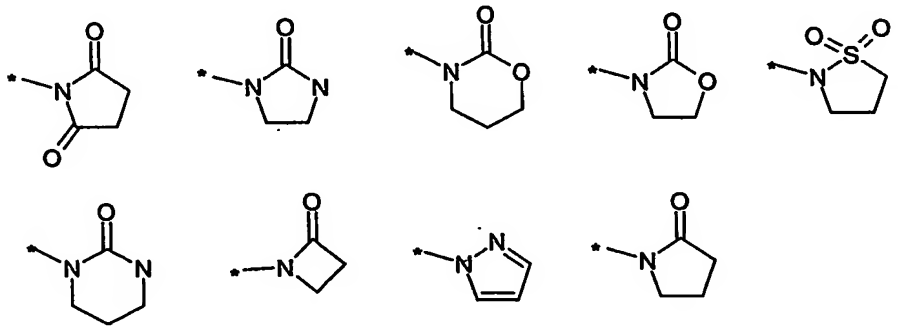


(IIb)

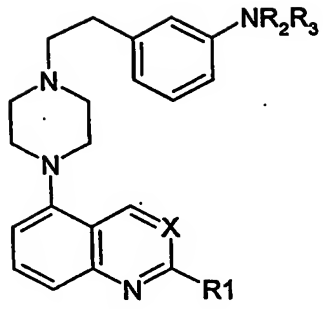
wherein A is oxygen or sulfur, D is $-(CH_2)_r-$, $-(CH_2)_rO-$ or $-O(CH_2)_r-$ wherein r is 0, 1, 2, 3, or 4, and E is C_{1-6}alkyl, an optionally substituted C_{3-7}cycloalkyl or an optionally substituted aryl.

8. A compound as claimed in any of claims 1-6, wherein R2 and R3, together with the nitrogen atom to which R2 and R3 are attached, combine to form a 4-6 membered monocyclic hetercyclic group, optionally substituted by one or more oxo.

9. A compound as claimed in claim 8, wherein R2 and R3 combine to form a group seleted from:



10. A compound as claimed in claim 1, having a general formula (Ia) :



(Ia)

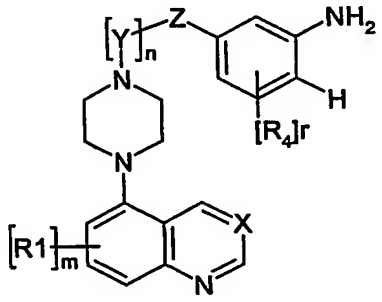
wherein X, R1, R2 and R3 are as defined in claim 1.

11. A compound as claimed in claim 1, which is:

- 3-(3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}phenyl)-1,3-oxazolidin-2-one;
- *N*-(3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}phenyl)-*N'*-phenylurea;
- *N*-[2-(methyloxy)phenyl]-*N'*-(3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}phenyl)urea;
- 1-(3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}phenyl)-2-imidazolidinone;
- 2,4-dimethyl-*N*-(3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}phenyl)-1,3-thiazole-5-carboxamide;
- *N*-(3-{1-hydroxy-2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}phenyl)-2,4-dimethyl-1,3-thiazole-5-carboxamide;
- 2-fluoro-*N*-(3-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}phenyl)benzamide;

or a pharmaceutically acceptable salt thereof.

12. A process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt thereof, which process comprises reacting a compound of formula (III):



(III)

wherein R1, m, X, Y, n, Z, R4 and r are as defined in any of claims 1-11, with compound(s) containing appropriate functional group(s) which is/are capable of reacting with a compound of formula (III) to form a compound as defined in any of claims 1-11; and thereafter optionally:

- removing any protecting group(s) and/or
- converting a compound of formula (I) into another compound of formula (I) and/or
- forming a pharmaceutically acceptable salt.

13. A compound as claimed in any of claims 1-11 for use as a therapeutic substance.

14. A compound as claimed in any of claims 1-11 for use in the treatment of a CNS disorder.

15. A compound as claimed in claim 14, wherein the disorder is depression or anxiety.

16. A method of treatment of a CNS disorder in a mammal including a human, which comprises administering to the sufferer a therapeutically safe and effective amount of a compound as claimed in any of claims 1-11.

17. A method as claimed in claim 16, wherein the disorder is depression or anxiety.

18. Use of a compound as claimed in any of claims 1-11 in the manufacture of a medicament for use in the treatment of a CNS disorder.

19. Use as claimed in claim 18, wherein the disorder is depression or anxiety.

20. A pharmaceutical composition comprising a compound as claimed in any of claims 1-11, and a pharmaceutically acceptable carrier or excipient.

21. A process for preparing a pharmaceutical composition as defined in claim 20, the process comprising mixing a compound as claimed in any of claims 1-11 and a pharmaceutically acceptable carrier or excipient.